Syntheses and Ring-Closures of Difunctional Tetrahydroisoquinolines

PhD Thesis

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CONTENTS

ABBREVIATIONS AND SYMBOLS

Ac	=	Acetyl
AF	=	Accumulation factor
Ar	=	Aryl
Boc	=	*tert*-Butoxycarbonyl
Cbz	=	Carbobenzyloxy
DBU	=	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	=	Dicyclohexyl carbodiimide
DEAD	=	Diethyl azodicarboxylate
DME	=	1,2-Dimethoxyethane
DMF	=	Dimethylformamide
DOPA	=	Dihydroxyphenylalanine
Et	=	Ethyl
Fmoc	=	9-Fluorenyl methoxycarbonyl
GIAO	=	Gauge-including atomic orbital
HEI	=	High-energy intermediate
HEIA	=	High-energy intermediate analogue
HF	=	HARTREE-FOCK
^3J	=	Vicinal scalar coupling constant
K	=	[ring]/[chain]
MDR	=	Multidrug resistance
Me	=	Methyl
MEM	=	β-Methoxyethoxymethyl
NMR	=	Nuclear magnetic resonance
MRP1	=	Multidrug resistance protein 1
NOE	=	Nuclear OVERHAUSER effect
NOESY	=	Nuclear OVERHAUSER effect spectroscopy
P	=	Population
P-gp	=	Plasma glycoprotein
Ph	=	Phenyl
Phth	=	Phthaloyl
ppm	=	Parts per million
Red-Al	=	Sodium bis(2-methoxyethoxy)aluminium hydride
r.t.	=	Room temperature
TBAF	=	Tetrabutylammonium fluoride
TBS	=	*tert*-Butyldimethylsilyl
THF	=	Tetrahydrofuran
TIC	=	1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid
TMS	=	Tetramethylsilane
Tos	=	*para*-Toluenesulfonyl
δ	=	Chemical shift
ρ	=	Reaction constant
σ^+	=	HAMMETT-BROWN parameter

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1. INTRODUCTION

The isoquinoline skeleton is a heterocyclic ring system that frequently occurs among both natural and synthetic bioactive molecules. Isoquinoline derivatives are applied for many therapeutic purposes. On the basis of the spasmolytic activity of the benzylisoquinoline alkaloid papaverine (**1**), many synthetic analogues have been developed (*e.g.* drotaverine, ethaverine, moxaverine and dimoxyline). The antitussive noscapine (**2**) and the expectorant emetine are also naturally-occurring isoquinoline derivatives with current pharmaceutical applications. The list of synthetic isoquinoline derivatives of practical pharmacological importance includes the angiotensin-converting enzyme inhibitor quinapril (**3**) and moexipril, the local anaesthetic quinisocaine (**4**), the anthelminthic praziquantel (**5**), the antidepressant nomifensine and the antiviral nelfinavir (**6**) (Fig. 1).[1]

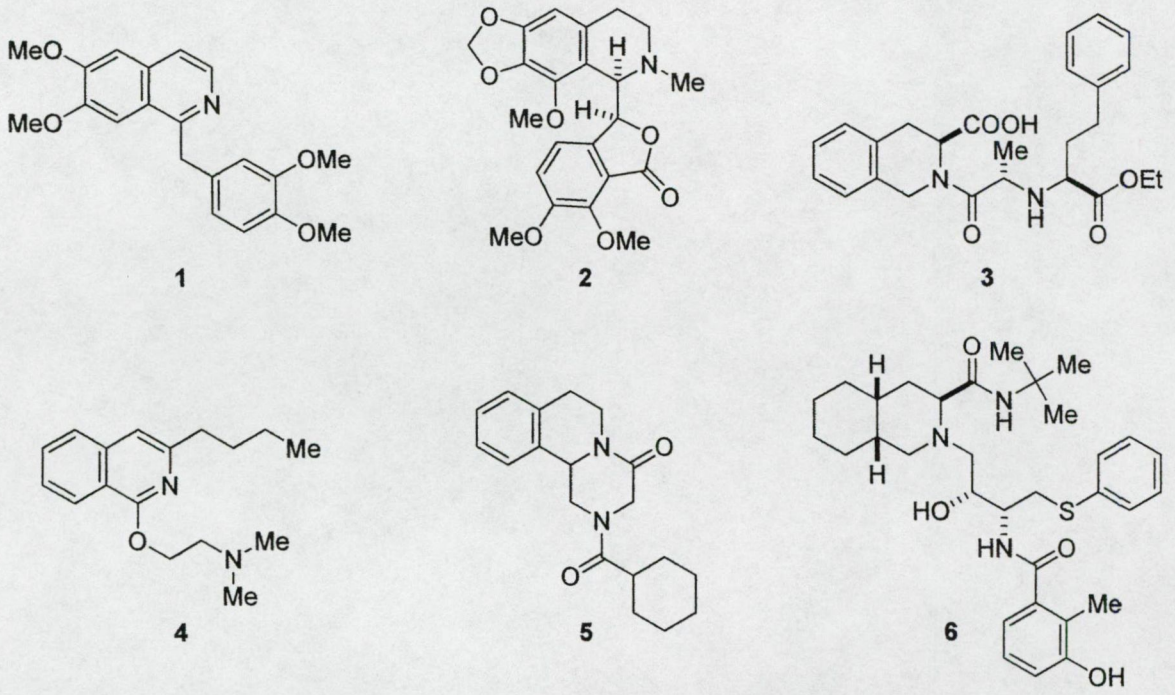
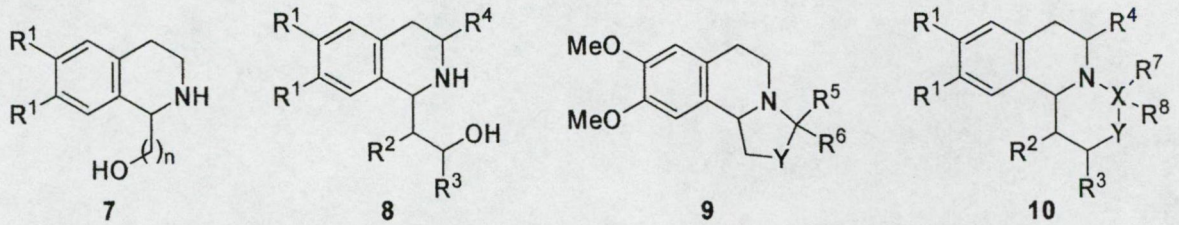


Figure 1

The frequent occurrence of the isoquinoline nucleus in alkaloids and in some physiologically active compounds has led to considerable interest in the synthesis of variously fuctionalized and saturated isoquinoline derivatives.[2-4] Asymmetric methods have also been developed for the preparation of enantiomerically pure derivatives [5]

The synthesis and transformations of 1,2,3,4-tetrahydroisoquinoline derivatives have been a research topic at the Institute of Pharmaceutical Chemistry, University of Szeged, in recent decades. During this work, numerous tetrahydroisoquinoline 1,2- and 1,3-amino alcohols (**7** and **8**) have been prepared and cyclized to the corresponding tetrahydroiso-

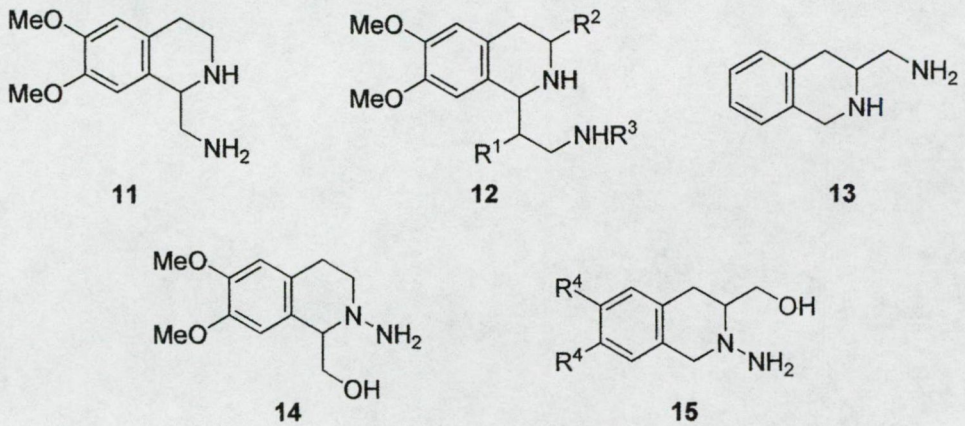
quinoline-condensed five- and six-membered 1,3- and 1,2,3-heterocycles (**9** and **10**) (Fig. 2). The conformations of the prepared tricycles were found to be strongly influenced by the steric effects of the substituents and the configurations of the substituted atoms. Some of the prepared derivatives proved to possess valuable pharmacological properties (*e.g.* antihypertensive, antiarrhythmic and antihypoxic effects).[6-15]



R^1 = H, OMe, OEt; R^2 = H, Me, Ph, CH_2OH; R^3 = H, C_1-C_4-alkyl; Ph; R^4 = H, Me; R^5, R^6 = H_2; O; N-aryl; H, aryl; R^7, R^8 = H_2; O; *N*-aryl; H, aryl; O_2; O, electron pair; O, Cl; O, Ph; O, $N(CH_2CH_2Cl)_2$; X = C, S, P; Y = O, S; n = 1, 2, 3, 4, 5

Figure 2

The aim of my PhD work was to study tetrahydroisoquinoline 1,2- and 1,3-diamines (**11-13**) and tetrahydroisoquinoline 1,2-hydrazino alcohols (**14** and **15**), which are the aza analogues of the previously investigated tetrahydroisoquinoline amino alcohols (Fig. 3). We planned to devise convenient synthetic methods for the preparation of variously substituted derivatives, and to study the synthetic applicabilities of **11-15** in cyclization reactions with a view to obtaining isoquinoline-condensed heterocycles.



R^1 = H, Me; R^2 = H, Me; R^3 = H, Me, Ph; R^4 = H, OMe

Figure 3

The aim of these transformations was to collect data relating to the scope and limitations of the effects influencing the steric structure and the ring-chain tautomeric character

of the isoquinoline-condensed, saturated 1,3- and 1,2,3-heterocycles. The synthesis of certain diamine derivatives for pharmacological studies was also planned.

Details of the syntheses, physical and analytical data on the new compounds described in the thesis, and descriptions of the NMR spectroscopic analyses of the tautomeric equilibria are to be found in the experimental part of the enclosed publications.

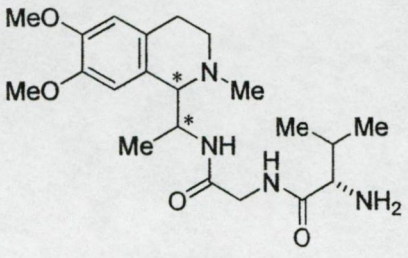
The references to the publications relating to my own research are given as Roman numerals; other literature references are given as Arabic numerals as superscripts.

2. LITERATURE

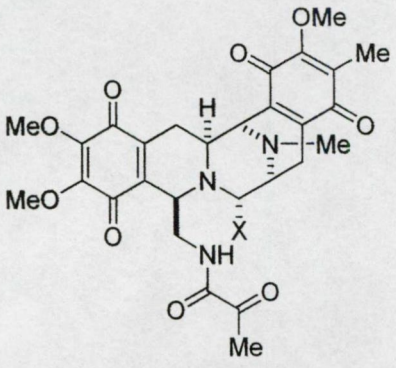
In the literature part of my PhD thesis, I would like to summarize the most important synthetic methods and transformations of 1-aminoalkyltetrahydroisoquinolines. To collect chemical information related to the subject, the SciFinder and Beilstein databases were used. Due to the limited size of the thesis, data on the chemistry and the various synthetic applications of 1-aminoaryltetrahydroisoquinolines[16-18] are omitted from this compilation.

2.1. Synthesis of 1-aminoalkyltetrahydroisoquinolines

The synthesis of 1-aminoalkyl-substituted 1,2,3,4-tetrahydroisoquinolines is of interest since this moiety can be found in natural compounds such as amphibin I (**16**), and saframycins (**17** and **18**). The natural amphibin I (**16**), the alkaloid of *Ziziphus amphibia*, A. Cheval, is a mixture of two diamine diastereomers, one of which has the 1*R*,9*S* and the other the 1*S*,9*R* configuration (the valine in the side-chain has the *S* configuration in both isomers).[19] Saframycins (**17** and **18**) are naturally-occurring antiproliferative agents which have been isolated from bacterial sources (*e.g. Streptomyces lavendulae*) and marine sponges.[20] The syntheses of these bisquinone alkaloids could be accomplished through tetrahydroisoquinoline intermediates.



amphibin I: **16**



X = CN: saframycin A: **17**
X = H: saframycin B: **18**

Figure 4

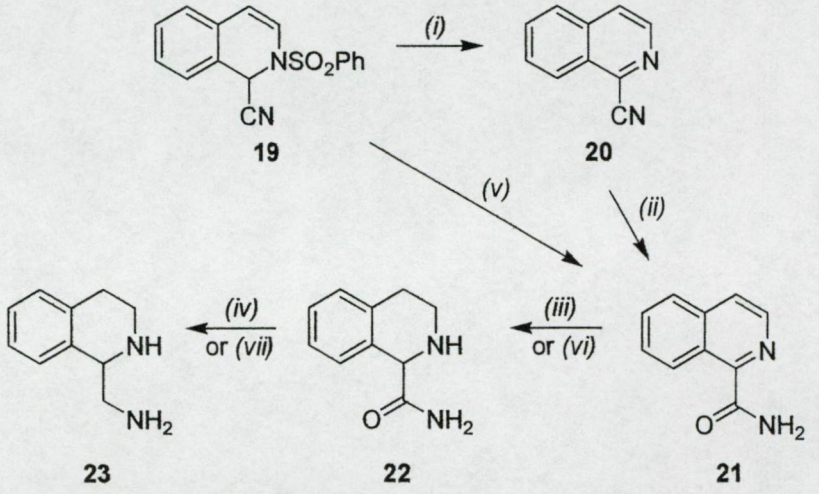
The main synthetic methods that have been applied for the preparation of 1-aminoalkyl-substituted 1,2,3,4-tetrahydroisoquinolines can be classified according to the sequence of the formation of the amino functional group and the isoquinoline ring. Reduction methods involve constructions of the amino group from the corresponding nitrile, carboxamide, azide or nitro derivatives of differently saturated isoquinolines. In some cases, the amino function is built into the side-chain by the substitution of an appropriate leaving

group. In the methods based on isoquinoline ring construction through the use of amino-containing building blocks, the BISCHLER-NAPIERALSKI and the PICTET-SPENGLER cyclizations are applied, starting from the corresponding amino acids or amino aldehydes.

2.1.1. Reductions of isoquinoline-1-carboxylic acid derivatives

Through the reductions of *N*-containing derivatives of tetrahydroisoquinoline amino acids (nitriles or amides), the corresponding diamines could be obtained. Amides are usually reduced with $LiAlH_4$, while nitriles can be reduced by using hydrogen developed during alcoholate formation with Na[21,22] by catalytic hydrogenation[23] or by using $LiAlH_4$[24] as a reducing agent. Starting from substituted carboxamides, *N*-substituted diamines could be obtained.[25,26]

JONES *et al.* accomplished the synthesis of diamine **23** via an amide intermediate, starting from the REISSERT compound of sulfonamide type **19**. By reduction with $NaBH_4$, dihydroisoquinoline **19** was converted into 1-isoquinolinecarbonitrile (**20**), which was hydrolysed to the carboxamide **21**. Catalytic reduction of the pyridine ring of **21** resulted in tetrahydroisoquinoline **22**, the carboxamide substituent of which was converted to the corresponding aminomethyl group by using diborane generated *in situ* (Scheme 1).[27]

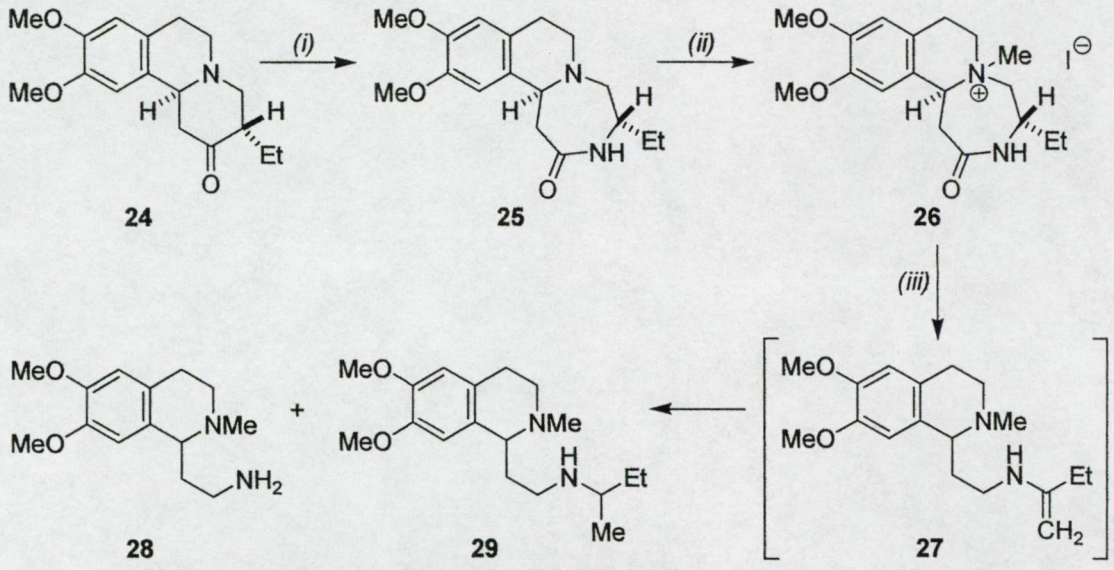


Reagents and conditions: *(i)*: $NaBH_4$, EtOH, r.t., 2 h, 100%; *(ii)*: KOH, H_2O_2, 40 °C, then r.t., 1.5 h, 82%; *(iii)*: PtO_2, H_2, 70% EtOH, HBr, 20 atm, r.t., 2 h, 95%; *(iv)*: $BF_3.OEt_2$, $NaBH_4$, THF, 0 °C, 20 min, reflux, 12 h, 100%; *(v)*: 50% NaOH, 100 °C, 8 min, 95%; *(vi)*: 1. HBr, C_6H_6, 10 min, 97%; 2. PtO_2, H_2, 70% EtOH, 3 atm, 78%; *(vii)*: $LiAlH_4$, THF, reflux, 8 h, 30%.

Scheme 1

KATZ and POPP converted amide **21**, obtained directly from the REISSERT compound **19** by alkaline treatment, to diamine **23** by sequential reductions of the aromatic ring and the carboxamide function.[28]

Reductive ring-opening of isoquinoline-condensed cyclic carboxamides may lead to tetrahydroisoquinoline diamines. When BEGLEY and WHITTAKER reduced the quaternary 1,4-diazepino[7,1-*a*]isoquinolin-2-one derivative **26**, obtained by a SCHMIDT rearrangement and a subsequent quaternization, starting from benzo[*a*]quinolizin-2-one **24**, with Red-Al, they found that the initial reduction of the amide function was followed by a HOFMANN elimination.



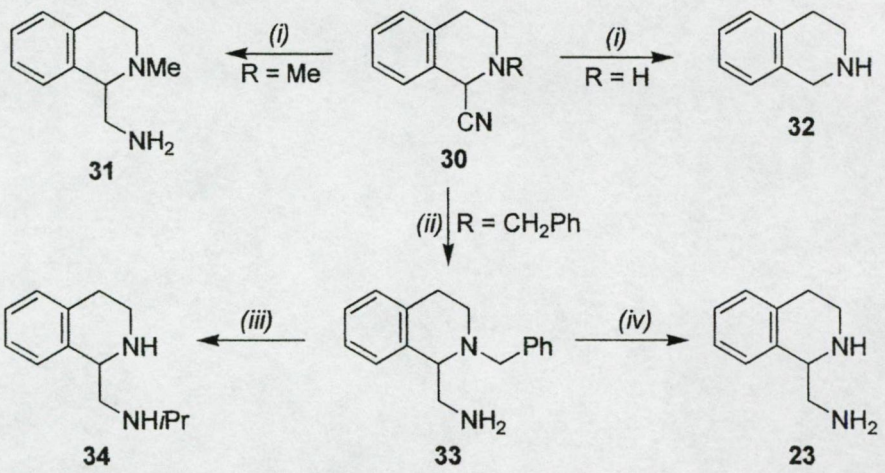
Reagents and conditions: (i): NaN_3, H_2SO_4, 0 °C, then **24**, $CHCl_3$, 90%; *(ii)*: MeI, AcOH, reflux, 1 h, 98.5%; *(iii)*: Red-Al, THF, reflux, 2.5 h.

Scheme 2

The enamine intermediate **27** was reduced further to 1-(2-aminoethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**28**) as the major, and its *N*-(2-butyl)-substituted derivative **29** as the minor product. Compounds **28** and **29** were separated by fractional crystallization and chromatographic methods (Scheme 2).[29]

To examine their β-adrenoceptor activity, BEAUMONT *et al.* synthetized the catecholamine analogue 1-(aminomethyl)tetrahydroisoquinolines by starting from 2-substituted 1-cyano-1,2,3,4-tetrahydroisoquinoline derivatives (**30**). While the *N*-methyl and the *N*-benzyl-substituted compounds (**30**, R = Me, CH_2Ph) could be conveniently reduced to the corresponding *N*-substituted diamines (**31** and **33**),[30,31] in an attempt to perform a similar transformation for the *N*-unsubstituted derivative (**30**, R = H), HCN elimination occurred and 1,2,3,4-tetrahydroisoquinoline (**32**) was obtained as the main product.[31]

The *N*-benzyl-substituted diamine could be applied both for the preparation of the *N*-unsubstituted diamine **23** (debenzylation) and for the synthesis of the isoproterenol analogue **34** (reductive alkylation prior to debenzylation) (Scheme 3).[31]



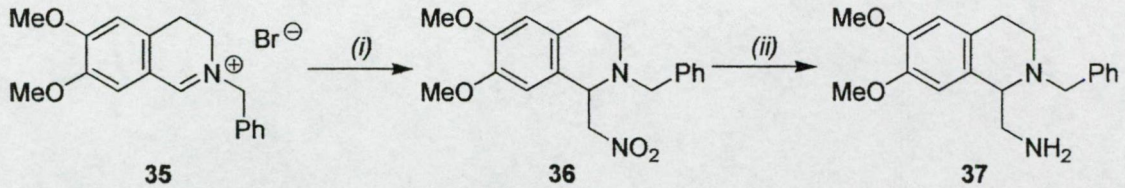
Reagents and conditions: *(i)*: $LiAlH_4$; *(ii)*: AlH_3, Et_2O, r.t., overnight, 88%; *(iii)*: 1. $NaBH_3CN$, HCl, MeOH, acetone, r.t., 16 h, 97%; 2. 5% Pd/C, H_2, 96% EtOH, HCl, 55%; *(iv)*: Pd/C, H_2, 96% EtOH, 1 atm, r.t, 24 h, then 50 °C, 12 h, 93%.

Scheme 3

2.1.2. Reductions of 1-nitroalkyl- or 1-azidoalkyl-substituted isoquinolines

Nitro and azido functions can be conveniently reduced to the corresponding amines and these reactions have been utilized in the preparation of *N*-substituted tetrahydroisoquinoline 1,2-diamines.

In 1925, HAWORTH and PERKIN tried to reduce the readily available 1-nitromethyl-tetrahydroisoquinolines, but their attempts were reported to be unsuccessful, resulting in the elimination of nitromethane with a variety of reducing agents (*e.g.* Zn, $SnCl_2$ and Na-Hg).[32] When BEAUMONT *et al.* investigated the $LiAlH_4$ reduction of the analogous 2-benzyl-6,7-dimethoxy-1-(nitromethyl)tetrahydroisoquinoline (**36**), they observed that the reaction conditions had a great influence on the yield.

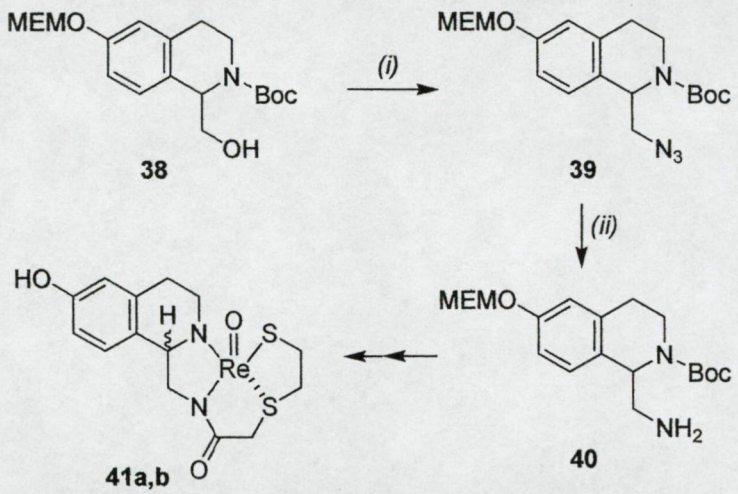


Reagents and conditions: *(i)*: CH_3NO_2, KOH, MeOH, r.t., 1 h, 84%; *(ii)*: 1. $LiAlH_4$, THF, reflux, 1 h, 16% (in a SOXHLET thimble: 85%); or 2. Red-Al, benzene, reflux, 1 h, 25%.

Scheme 4

When a "normal addition" procedure was applied (*i.e.* addition of a THF solution of **36** to a stirred suspension of $LiAlH_4$ in THF), the yield was only 16%, but when a solution of **36** in THF was refluxed beneath a SOXHLET thimble containing $LiAlH_4$ (*i.e.* a "reverse addition"), a dramatic increase in the yield (to 85%) was achieved (Scheme 4).[31]

Tetrahydroisoquinoline diamine **40** proved to be a key intermediate in the synthesis of an oxorhenium(V) complex (**41**) mimic of a steroidal oestrogen. Compound **40** was prepared by a transformation of the hydroxy function of the corresponding amino alcohol analogue **38**. Treatment of **38** with diphenylphosphoryl azide under MITSUNOBU conditions resulted in the azide **39**, which was hydrogenated in the presence of Pd catalyst to the amine **40**. The *syn* and *anti* isomers of the tetradentate oxorhenium(V) complex **41** were separated by flash chromatography and both of them proved to exhibit a higher lipophilicity than that of oestrogen, while they bound only weakly to the oestrogen receptor (Scheme 5).[33]



41a: Hα; **41b**: Hβ

Reagents and conditions: (i): $(Ph)_3P$, DEAD, THF, 0 °C, 15 min, then **38**, $(PhO)_2PON_3$, r.t., 12 h, 91%; *(ii)*: 10% Pd/C, EtOH, H_2, r.t., 21 h, 84%.

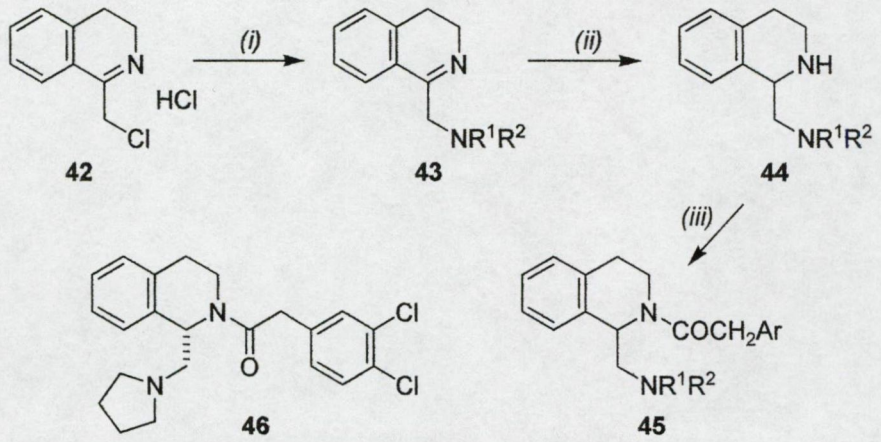
Scheme 5

2.1.3. Substitutions in the side-chain by nitrogen-containing nucleophiles

I shall now discuss the substitution reactions of 1-(haloalkyl)- or 1-(hydroxyl)-substituted isoquinoline derivatives with the appropriate *N*-containing agents, when no further transformation or only a hydrolytic step (*but no reduction*) is required to construct the amino function in the side-chain.

In consequence of the activated leaving group at the α-position of the side-chain, 1-(α-haloalkyl)-3,4-dihydroisoquinolines are convenient starting materials for nucleophilic substitutions with amines to yield di- or tetrahydroisoquinoline diamines. The substitution reactions of 1-(chloromethyl)-3,4-dihydroisoquinoline (**42**) with acyclic or cyclic primary or secondary amines gave diamines **43** in good yields, which were then reduced to the corresponding tetrahydro derivatives **44** with $NaBH_4$. Some of the *N*-arylacetylated diamines **45** proved to exhibit κ opioid analgesic activities. The pyrrolidine derivative with the *S*

configuration (**46**) had a 100-fold higher κ receptor-binding affinity than that of morphine (Scheme 6).[34]



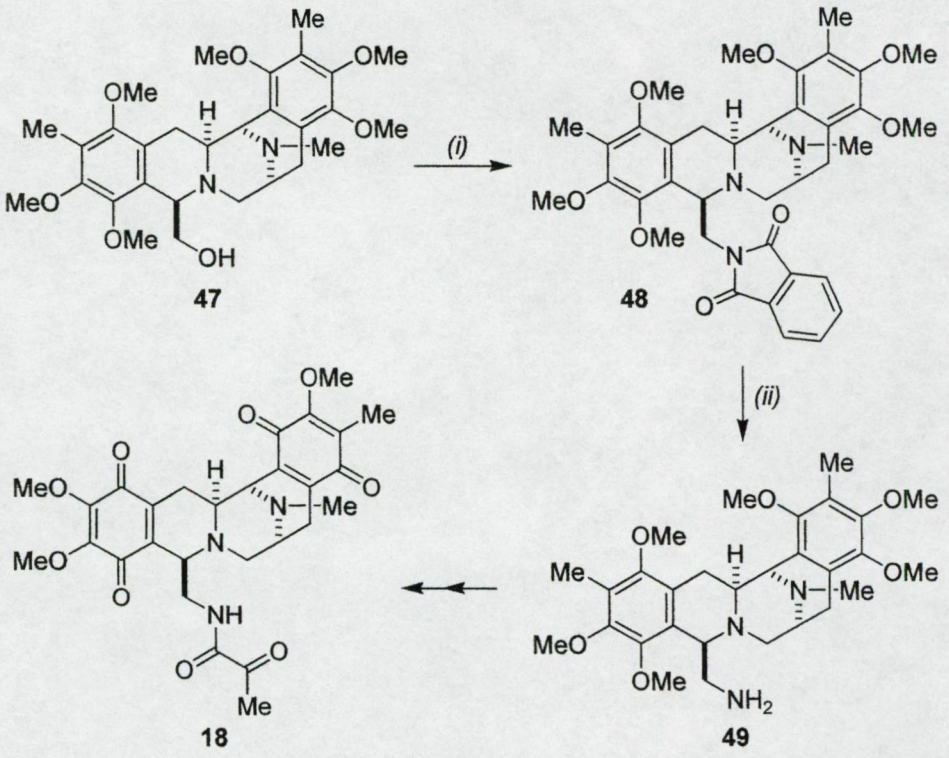
R^1, R^2 = H, Me, Et, *n*Pr, -$(CH_2)_4$-, -$(CH_2)_5$-; Ar = 2-NO_2-Ph, 3-NO_2-Ph, 4-NO_2-Ph, 4-Br-Ph, 4-CF_3-Ph, 3,4-Cl_2-Ph

Reagents and conditions: *(i)*: NHR^1R^2, MeOH, 0 °C, then r.t., overnight; *(ii)*: $NaBH_4$, MeOH, 0 °C, 2 h, 46-80% (*i*+*ii*); *(iii)*: $ArCH_2COCl$, K_2CO_3, CH_2Cl_2, 0 °C, 3 h.

Scheme 6

The above methodology was successfully applied by GRIFFITH *et al.* in the transformations of 1-(chloromethyl)-4-phenyl-3,4-dihydroisoquinoline. By nucleophilic substitution with primary or secondary amines, 4-phenyl-substituted analogues of **43** were obtained, which were reduced to the corresponding tetrahydro derivatives. Due to the 4-phenyl substituents, *cis* and *trans* isomers were formed, which were readily separated by fractional crystallization. The catalytic hydrogenation proved to be highly selective (*cis* : *trans* = ~10 : 1) for the formation of the *cis* isomer.[35-37]

The total synthesis of the antitumour antibiotic saframycin B (**18**) could be accomplished via a tetrahydroisoquinoline diamine intermediate (**49**), which was obtained from a 1-(hydroxymethyl)-substituted tetrahydroisoquinoline derivative (**47**) under MITSUNOBU conditions. When **47** was treated with diethylazodicarboxylate (DEAD), triphenyl-phosphine and phthalimide, phthalimidomethyl-substituted compound **48** was obtained, the phthaloyl group of which was removed by hydrolysis with hydrazine hydrate. Diamine **49** was converted in two steps to racemic saframycin B (**18**) (Scheme 7).[38-39]



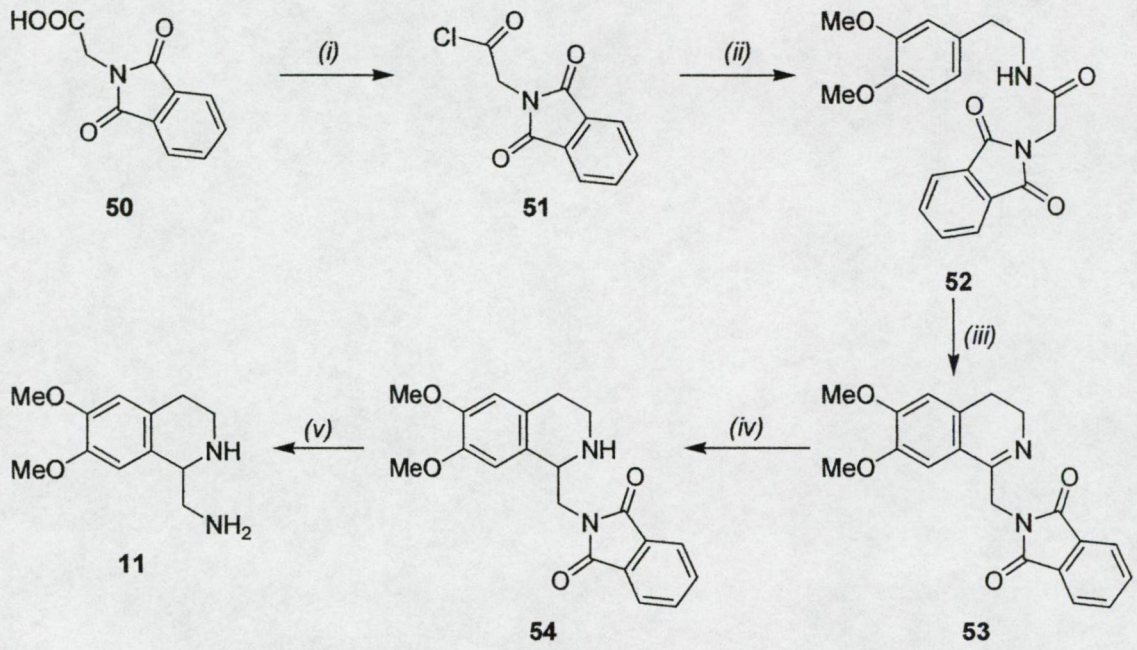
Reagents and conditions: (i): DEAD, PhthNH, PPh_3, THF, r.t., 100%; *(ii)*: $H_2NNH_2.H_2O$, EtOH, reflux, 90%.

Scheme 7

2.1.4. Methods based on the BISCHLER-NAPIERALSKI ring-closures of amino acid derivatives

Probably the method most frequently used for the synthesis of isoquinolines is the BISCHLER-NAPIERALSKI reaction, which consists in the cyclodehydration of *N*-acyl derivatives of β-phenylethylamines with LEWIS acids such as $POCl_3$ or P_2O_5 pentoxide and affords 3,4-dihydroisoquinolines. Starting from β-phenylethylamides of amino acid derivatives bearing an appropriate protecting group on the basic nitrogen, 1-(aminoalkyl)-substituted 3,4-tetrahydroisoquinolines could be obtained, the reduction (and *N*-deprotection) of which results in tetrahydroisoquinoline diamines.

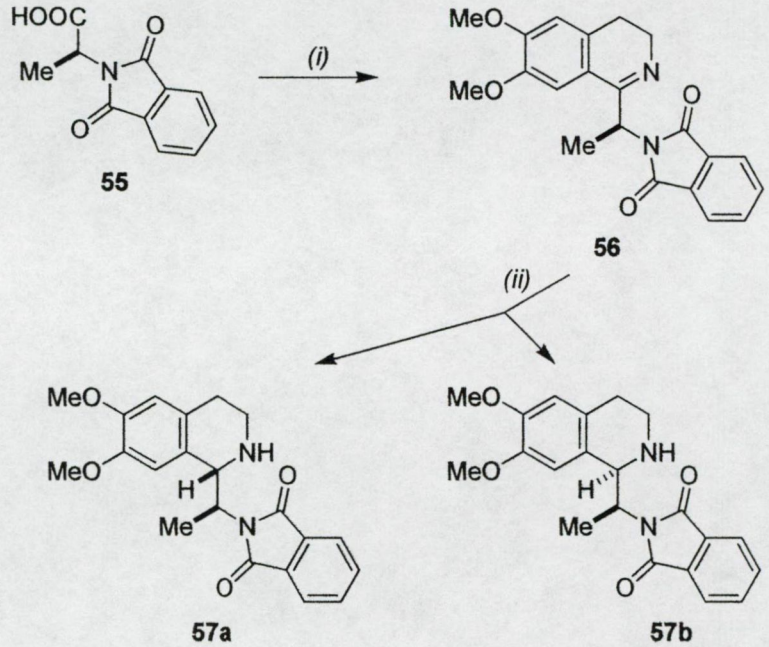
This method was first applied for the synthesis of a tetrahydroisoquinoline 1,2-diamine (**11**) by HARWOOD and JOHNSON in 1933. The amide **52**, obtained from the *N*-phthaloylglycyl chloride and homoveratrylamine, was cyclized with $POCl_3$ in toluene to yield dihydroisoquinoline **53**. The double bond of **53** was reduced by catalytic hydrogenation and the phthaloyl protecting group of **54** was removed by hydrazinolysis (Scheme 8).[40] Ring-closure of the phenyl analogue of **52**, without the activating methoxy groups, proceeded with a considerably lower yield.[41]



Reagents and conditions: (i): $SOCl_2$, 77%; *(ii)*: homoveratrylamine, Na_2CO_3, 72%; *(iii)*: $POCl_3$, toluene, reflux, 1.5 h, 87%; *(iv)*: PtO_2, H_2, 3 atm; *(v)*: $H_2NNH_2.H_2O$, EtOH.

Scheme 8

N-Phthaloylamino carboxamides of type **52**, the starting materials for the BISCHLER-NAPIERALSKI cyclization, can alternatively be obtained by the *N*-alkylation of potassium phthalimide with the corresponding *N*-chloroalkanoyl β-phenylethylamines[42-44]



Reagents and conditions: *(i)*: 1. homoveratrylamine, *N*-hydroxysuccinimide, DCC, $CHCl_3$, 20 °C, 12 h, 94%; 2. P_2O_5, $CHCl_3$, -30 °C, then 0 °C, 24 h, 85%; *(ii)*: $NaBH_3CN$, HCl, MeOH, r.t., 30 min., 67% (**57a**), 16% (**57b**).

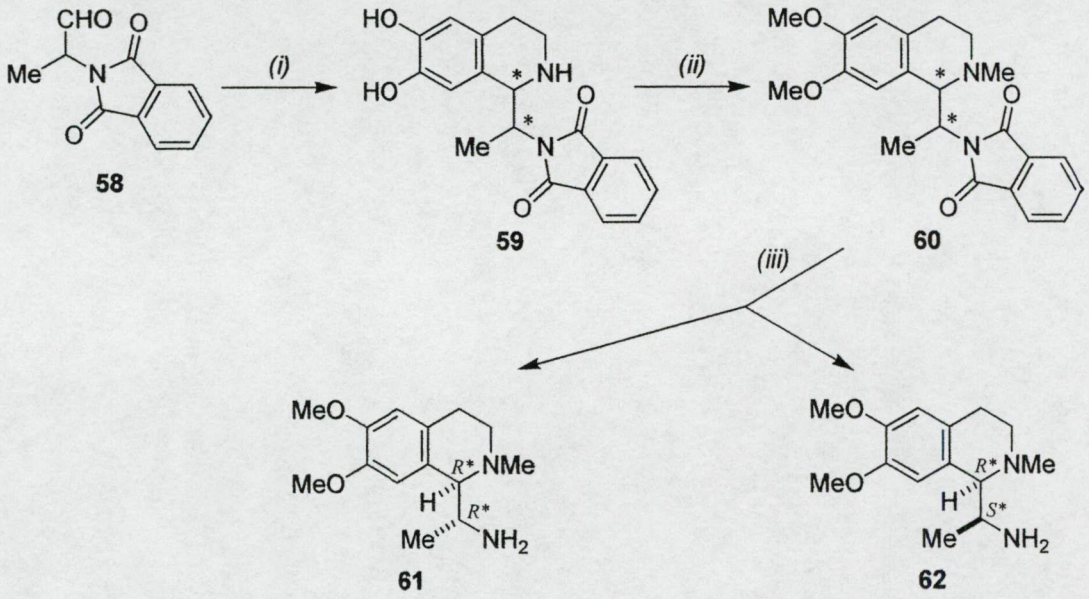
Scheme 9

BISCHLER-NAPIERALSKI ring-closure of the amide obtained from *N*-phthaloyl-L-alanine (**55**) and homoveratrylamine was applied in the preparation of amphibin I (**16**) by TSCHESCHE *et al.* The $NaBH_3CN$ reduction of the dihydroisoquinoline **56** resulted in a 4 : 1 mixture of the diastereomers **57a** and **57b**, which were separated by chromatographic methods. Considerable racemization of the chirality centre of L-alanine could be avoided when a rapid reduction and work-up were employed immediately after ring-closure. Compounds **57a** and **57b** were converted in four steps to (1*S*,9*R*)- and (1*R*,9*S*)-amphibin I (**16**) (Scheme 9).[19]

2.1.5. PICTET-SPENGLER cyclizations by using amino aldehydes

The PICTET-SPENGLER reaction is a condensation of β-phenylethylamines with carbonyl compounds in the presence of an acidic catalyst to give 1,2,3,4-tetrahydroisoquinolines. By choosing an appropriate carbonyl component, such as an *N*-protected amino aldehyde, this method can be utilized for the synthesis of tetrahydroisoquinoline diamines.

Condensation of racemic *N*-phthaloyl alaninal (**58**) with dopamine hydrochloride in methanol resulted in a diastereomeric mixture of tetrahydroisoquinolines (**59**), which were *O*-methylated with diazomethane and then *N*-methylated by using ESCHWEILER-CLARKE conditions. Diastereomers of **60**, separated by preparative thin-layer chromatography, were converted to diamine diastereomers **61** and **62** by hydrazinolysis of the phthaloyl moiety.

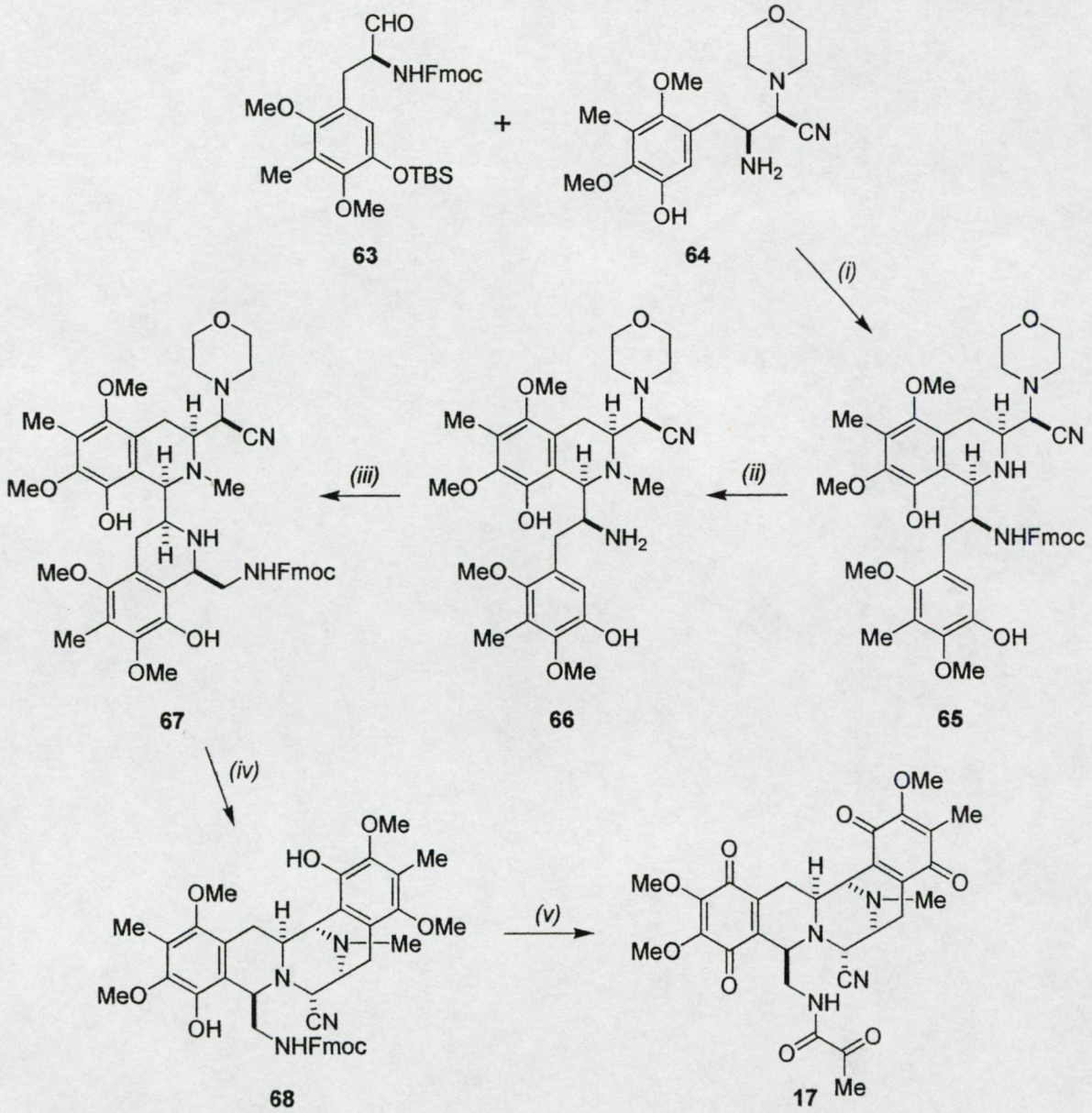


Reagents and conditions: (i): dopamine hydrochloride, MeOH, Ar, r.t., 7 days, 37%; *(ii)*: 1. CH_2N_2; 2. HCHO, HCOOH; *(iii)*: 1. preparative thin-layer chromatography; 2. $H_2NNH_2.H_2O$.

Scheme 10

Diamines **61** and **62** were resolved by using di-(*p*-toluyl)-L- or -D-tartaric acid, and all of the possible stereoisomers of amphibin I (**16**) were synthetized from the four diamine enantiomers (Scheme 10).[45]

The PICTET-SPENGLER reaction of the *N*-Fmoc-protected L-alaninal and L-DOPA hydrochloride gave 1-aminomethyl-α-methyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid diastereomers, the 1*S*,3*S*,1'*S* isomer of which proved to be a good β-turn dipeptide mimetic.[46]



Reagents and conditions: (i): 1. Na_2SO_4, CH_2Cl_2, r.t., >90%; 2. LiBr, DME, 35 °C, 65-72%; *(ii)*: 1. CH_2O-H_2O, $NaBH(OAc)_3$, MeCN, r.t., 94%; 2. AcOH, TBAF, THF, r.t.; 3. DBU, CH_2Cl_2, r.t., 92%; *(iii)*: *N*-Fmoc-glycinal, Na_2SO_4, CH_2Cl_2, r.t., 66%; *(iv)*: $ZnCl_2$, Me_3SiCN, CF_3CH_2OH-THF, r.t., 86%; *(v)*: 1. DBU, CH_2Cl_2, r.t., 88%; 2. $ClCOCOCH_3$, $PhNEt_2$, CH_2Cl_2, 0 °C, 89%; 3. PhIO, MeCN-H_2O, 0 °C, 66%.

Scheme 11

MYERS and KUNG described a short and enantioselective synthetic route to the potent antitumour agent (–)-saframycin A (**17**) with tetrahydroisoquinoline diamine intermediates obtained by PICTET-SPENGLER cyclization. In the first step, the enantiomerically pure *N*- and *C*-protected α-amino-aldehydes (**63** and **64**, respectively) were condensed to give the *cis*-tetrahydroisoquinoline (**65**) as the main product (a 5 : 1 mixture of the *cis* and *trans* isomers was formed, which was separated by flash chromatography). By *N*-methylation and removal of the *N*-Fmoc protecting group of **65**, a tetrahydroisoquinoline diamine (**66**) was obtained, the PICTET-SPENGLER cyclization of which with *N*-Fmoc-glycinal was accomplished with good *cis*-selectivity to yield **67**. Compound **67** was converted to the pentacyclic intermediate **68**, which was transformed in three steps to (–)-saframycin A (**17**) (Scheme 11).[47]

The MYERS group devised a solid-phase version of the above procedure, which proved to be suitable for the preparation of a great number of saframycin analogues with wide-ranging structural diversity.[48,49]

By PICTET-SPENGLER cyclizations of *N*-arylsulfonyl-β-phenylethylamines and 3-(phthaloylamino)propanal and subsequent removal of the phthaloyl group, BARN *et al.* prepared 1-(2-aminoethyl)-2-arylsulfonyl-1,2,3,4-tetrahydroisoquinolines, by *N*-acylations of which tetrahydroisoquinoline sulphonamide-based libraries were synthetized both in solution and in the solid phase. Some of the prepared compounds exhibited δ-opioid receptor activity.[50,51]

2.2. *Transformations of tetrahydroisoquinoline diamines*

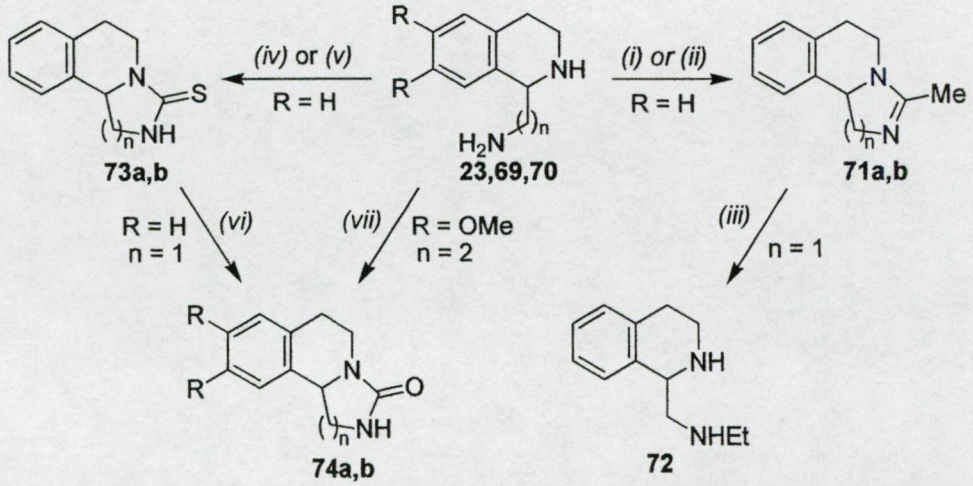
Although the diamine function provides various possibilities for further transformations, including *N*-substitution reactions, tetrahydroisoquinoline diamines are applied almost entirely for the synthesis of isoquinoline-condensed heterocycles. By insertion of a one-carbon-containing unit, imidazo[5,1-*a*]- and pyrimido[6,1-*a*]isoquinolines are obtained. Tetrahydroisoquinoline 1,2-diamines have been used as the starting materials for the synthesis of pyrazino[2,1-*a*]isoquinoline derivatives. There are some examples of the conversion of tetrahydroisoquinoline 1,3-diamines to steroidal analogues containing nitrogens at positions 8 and 13 of the gonane skeleton (8,13-diazasteroids). Some heterocyclic derivatives of tetrahydroisoquinoline diamines proved to possess biological activities.

2.2.1. Imidazo[5,1-a]- and pyrimido[6,1-a]isoquinolines

Depending on the one-carbon-containing unit inserted between the amino groups of tetrahydroisoquinoline diamines, various derivatives of imidazo[5,1-*a*]- and pyrimido[6,1-*a*]isoquinolines can be obtained.

Ring-closures of **23** and **69** with imidate (for n = 1) or orthoester (for n = 2) result in cyclic amidine derivatives **71a,b**, respectively.[27,52] The $LiAlH_4$ reduction of 3-methyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline (**71a**) led not to the expected imidazolidine derivative, but to the 1-(ethylaminomethyl)-1,2,3,4-tetrahydroisoquinoline **72** (Scheme 12),[27] which can be explained by the ring-chain tautomeric character of the imidazolidine intermediate.

In the reactions of tetrahydroisoquinoline diamines **23** and **69** with carbon disulfide, dithiocarbamate salts are formed, which are converted to the corresponding cyclic thiourea derivatives **73a,b** on prolonged heating. *S*-Alkylation of 1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinoline-3(2*H*)-thione (**73a**) with chloroacetic acid yielded an isothiuronium salt intermediate, hydrolysis of which afforded the cyclic urea **74a**.[28] The analogous cyclic urea of pyrimidoisoquinoline of type **74b** was obtained by treatment of **70** with diethyl carbonate in the presence of NaOEt (Scheme 12).[53]



R = H, n = 1: **23**; R = H, n = 2: **69**; R = OMe, n = 2: **70**; n = 1: **71a**; n = 2: **71b**; n = 1: **73a**; n = 2: **73b**; R = H, n = 1: **74a**; R = OMe, n = 2: **74b**

Reagents and conditions: (i): ethyl acetimidate hydrochloride, EtOH, reflux, 3 h, 66%; *(ii)*: triethyl orthoacetate, BuOH, reflux, 15 h, 71%; *(iii)*: $LiAlH_4$, THF, reflux, 30 min, 86%; *(iv)*: 1. CS_2, NH_4OH, 50% EtOH, reflux, 4 h, then HCl, reflux, 18 h, 72%; *(v)*: CS_2, EtOH, r.t., 1.5 h, then DMF, reflux, 40 min, 95%; *(vi)*: 1: $ClCH_2COOH$, H_2O, reflux, 3 h, 99%; 2. NH_4OH, H_2O, 95%; *(vii)*: $(EtO)_2CO$, NaOEt, EtOH, reflux, 4 h, 64%.

Scheme 12

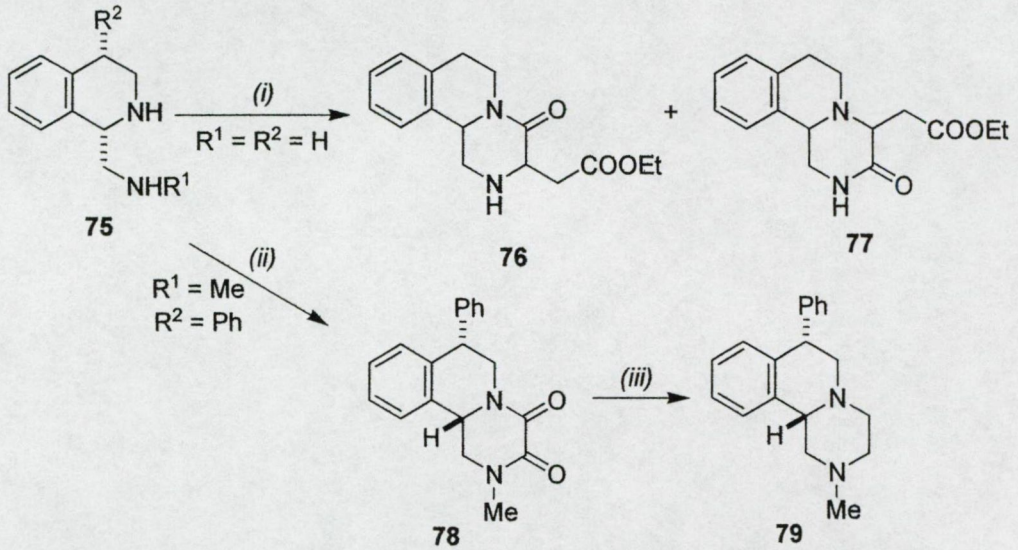
On cyclization of 1-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline (**24**) with bis(alkoxycarbonyl) derivatives of 2-methyl-2-thiopseudourea, 3-[(alkoxycarbonyl)amino]-1,5,6,10b-tetrahydroimidazo[5,1-*a*]isoquinolines were prepared.[54]

There is an example of the aldehyde ring-closure of a tetrahydroisoquinoline diamine (cyclic aminal formation): treatment of 1-[(phenylamino)methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline with formaldehyde resulted in 8,9-dimethoxy-3-phenyl-1,2,3,5,6,10b-hexahydroimidazo[5,1-*a*]isoquinoline.[25]

2.2.2. Pyrazino[2,1-a]- and 1,4-diazepino[7,1-a]isoquinolines

Cyclization of tetrahydroisoquinoline diamines with difunctional compounds (*e.g.* olefinic esters, haloalkylcarboxylic acid chlorides or diesters) results in pyrazino[2,1-*a*]- or 1,4-diazepino[7,1-*a*]isoquinolines. Since tetrahydroisoquinoline diamines contain non-equivalent nitrogens, when cyclizing agents containing two different functional groups are used, regioisomeric products are formed. To avoid the formation of regioisomers, *N*-protecting groups should be applied.[25]

When SHEKHTER *et al.* reacted the diamine **75** ($R^1 = R^2 = H$) with diethyl fumarate for the purpose of synthetizing praziquantel analogues, formation of the regiosomeric pyrazino[2,1-*a*]-isoquinolines (**76** : **77** = 3 : 2) was observed. The regioisomers were separated by fractional crystallization of their hydrochlorides. No concerning the relative configurations of **76** and **77** were reported (Scheme 13).[55]



Reagents and conditions: (i): diethyl fumarate, EtOH, r.t., 48h, 45% (**71**), 32% (**72**); *(ii)*: diethyl oxalate, $CHCl_3$, reflux, 4h, 77%; *(iii)*: BH_3, THF, reflux, 3h, 89%.

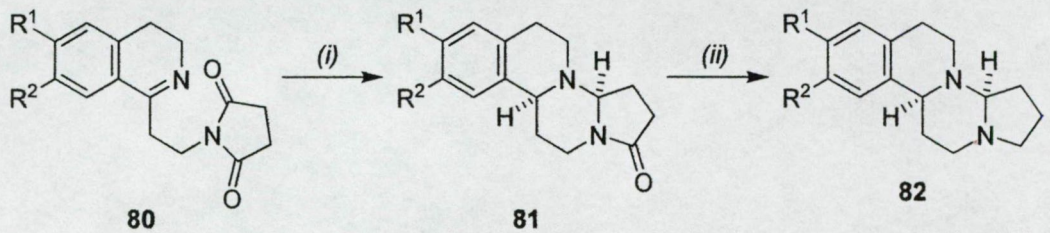
Scheme 13

The ring-closure of *cis*-1-(methylamino)methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**75**, R^1 = Me, R^2 = Ph) with diethyl oxalate in refluxing $CHCl_3$ gave the cyclic diamide **78**. Compound **78** was conveniently reduced with BH_3 to give the mianserin analogue pyrazino-[2,1-*a*]isoquinoline **79**, which was resolved with dibenzoyltartaric acid. In pharmacological evaluations, racemic **79** proved to possess excellent atypical antidepressant activity, which resides predominantly in the (+) isomer, while the (-) isomer was found to have antihistaminic activity.[35]

2.2.3. 8,13-Diazasteroids

The synthesis of steroid derivatives containing nitrogen atoms in various positions of the carbocyclic skeleton has gained wide attention in recent decades. The modified steroids containing nitrogen atoms in the carbocyclic skeleton are interesting compounds from a pharmacological aspect. Some 4-, 8- and 15-aza derivatives proved to exhibit antifungal activity, and 4-azasteroids (*e.g.* finasteride) have effects against benign prostatic hypertrophy.[56-58]

Tetrahydroisoquinoline diamines and their *N*-succinyl or *N*-phthaloyl intermediates are good starting materials for the preparation of diazasteroid derivatives. Catalytic hydrogenation of 6,7-substituted 1-(2-succinylaminoethyl)-3,4-dihydroisoquinolines (**80**) over PtO_2 resulted in 8,13-diazaoestrone derivatives **81** via a hemiaminal intermediate. [59-61] By reduction of the carboxamide function with $LiAlH_4$, 8,13-diazaoestrane derivatives **82** were obtained (Scheme 14; instead of the classical "steroidal" structures, azasteroids are depicted in the schemes in accordance with the drawings of tetrahydroisoquinoline diamines applied in the thesis). During the pharmacological tests, compounds **81** and **82** exhibited analgesic activity.



80 **81** **82**

R^1 , R^2 = H, Me, Cl, OMe, OCH_2Ph

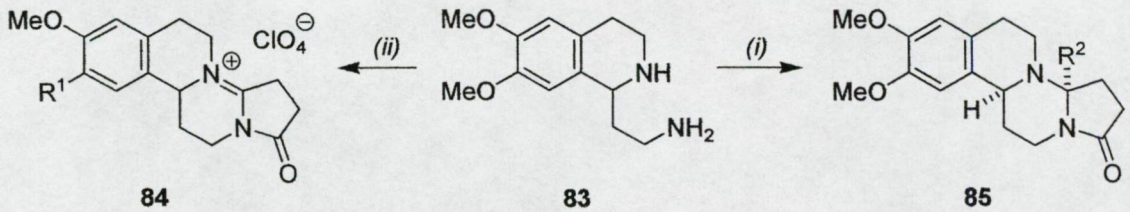
Reagents and conditions: (i): PtO_2, H_2, MeOH, r.t., 12 h, 69-76%; *(ii)*: $LiAlH_4$, THF, reflux, 66 h, 80%.

Scheme 14

The 8,13-diazaoestrane derivative **82** (R^1 = R^2 = OMe) was also prepared by reductive cyclizations of 1-[2-(3-oxo-1-pyrrolidinyl)ethyl]-1,2,3,4-tetrahydroisoquinoline. Through the use of a bulky reducing agent, $LiAlH[OCH(CH_3)tBu]_3$, formation of uncyclized by-products could

be diminished.[62] The reductive cyclization method was successfully applied in the case of 1-(2-phthaloylaminoethyl)-3,4-dihydroisoquinolines to yield 8,13-diazaoestrone derivatives containing a benzene ring attached to ring D of the steroidal skeleton.[63]

In the previous cases, the protecting groups of the nitrogen were built into the newly formed heterosteroid. Tetrahydroisoquinoline diamines can be converted to diazasteroid derivatives by domino ring-closures with difunctional reagents. This strategy was applied for the cyclizations of the diamine **83** with 3-ethoxycarbonylpropionimidate or with γ-oxo-acids, when 8,13-diazaoestrone derivatives (**84** and **85**) were formed (Scheme 15).[23,64] The ring-closure with γ-oxo-acids took place via ring-chain tautomeric pyrimido[6,1-*a*]isoquinoline intermediates, resulting in tetracycles **85** with excellent diastereoselectivities (Scheme 15).



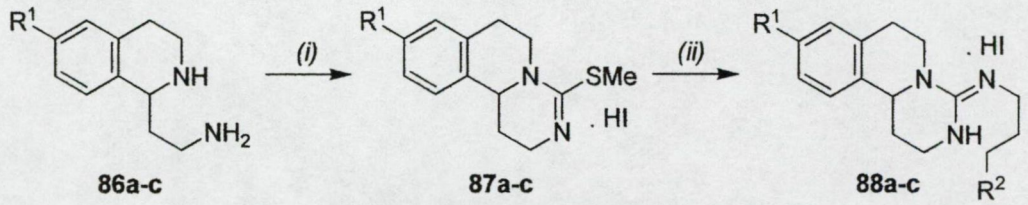
84 **83** **85**

R^1 = H, OMe; R^2 = Me, Ph,

Reagents and conditions: (i): 1. 3-ethoxycarbonylpropionimidate hydrochloride, 0 °C; 2. $HClO_4$; *(ii)*: $RCO(CH_2)_2COOH$, toluene, reflux, 1-2 h, 70-74%.

Scheme 15

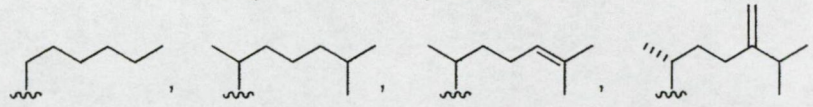
Inhibition of the synthesis of the fungal ergosterol causes serious malfunctions of the cell membrane, inhibition of the fungal growth, and cell death. Certain enzymes involved in ergosterol biosynthesis create carbocationic high-energy intermediates (HEIs). Compounds with structures similar to those of HEIs [*i.e.* high-energy intermediate analogues (HEIAs)], are able to act as inhibitors of fungal enzymes. GÖßNITZER *et al.* prepared some 8,13,15-triazasteroids and their 13,17-seco derivatives for the purpose of finding potential HEIAs as antifungal compounds.



86a-c **87a-c** **88a-c**

R^1 = H: **a**; R^1 = OH: **b**; R^1 = OMe: **c**

R^2:

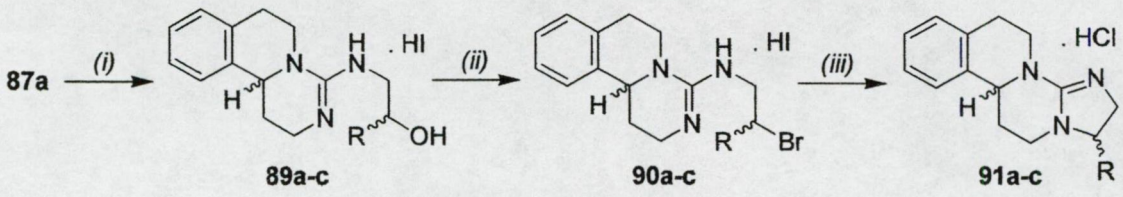


Reagents and conditions: (i): 1. CS_2, EtOH, r.t., 1.5 h, then DMF, reflux, 40 min; 2. MeI, MeOH, reflux, 1 h, 86% (**87a**), 49% (**87b**), 73% (**87c**); *(ii)*: $R^2(CH_2)_2NH_2$, THF, reflux, 12-16 h, 80-91%.

Scheme 16

Treatment of the 1-(β-aminoethyl)tetrahydroisoquinolines **86a-c** with CS_2 and subsequent methylation of the cyclic thiourea intermediates with methyl iodide gave the isothiuronium salts **87a-c**. When **87a-c** were reacted with alkyl- and alkenylamines, the N^4-substituted 4-iminopyrimido[4,3-*a*]isoquinolines (**88a-c**) were formed, which proved to be HEIAs with the structure of 8,13,15-triaza-13,17-secosteroids (Scheme 16). Compounds **88a** and **88c**, each with a saturated 3,7-dimethyl-branched octyl side chain, displayed the best inhibitory effects against the tested fungi. The inhibitory efficacy was better against yeasts and dermatophytes than that against the mould species.[44,65,66]

HEIAs with 8,13,15-triazasteroid structure were synthetized by transformations of the substitution of **87a**. On reaction with aminoalkanols, N^4-hydroxyalkyl-substituted 4-iminopyrimido[4,3-*a*]isoquinolines (**89a-c**) were formed, the hydroxy → bromo substitution of which was performed by using PBr_3. Intramolecular cyclizations of **90a-c** furnished the 8,13,15-triazasteroids **91a-c** (Scheme 17).[67]



R = H: **a**; R = hexyl: **b**; R = 1,5-dimethylhexyl: **c**

Reagents and conditions: (i): 2-aminoethanol (**a**), 1-amino-2-octanol (**b**), 1-amino-3,7-dimethyl-2-octanol (**c**), respectively, MeCN, reflux, 14-16 h, 71-87%; *(ii)*: PBr_3, CH_2Cl_2, -10 °C, 1h, then r.t., 15 h, 64-100%; *(iii)*: 1. NaH, THF, -10 °C, 1 h, then r.t., 20 h; 2. treatment with ethanolic HCl, 30-70%.

Scheme 17

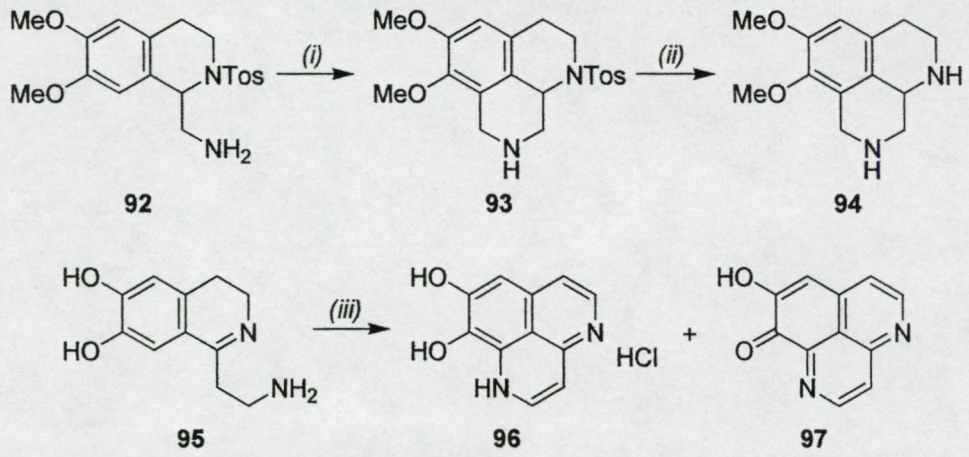
2.2.4. Other heterocycles

There are two examples when the ring-closure of a tetra- or dihydroisoquionoline diamine is directed toward the benzene ring by the lack of a substitutable hydrogen at the isoquinoline-nitrogen.

In the reaction of the *N*-tosylated diamine **92** with formaldehyde, the benzo[*d,e*][1,7]-naphthyridine derivative **93** was formed, the tosyl group of which was removed by using Na in liquid NH_3 (Scheme 18).[68]

When the phenolic 1-(2-aminoethyl)-3,4-dihydroisoquinoline derivative **95** was treated with peroxosulfate bisdemethyl-aaptamine (**96**) was obtained by oxidative cyclization besides minor amounts of its oxidation product **97**. Aaptamines are marine alkaloids with a 1*H*-benzo[*d,e*][1,6]naphthyridine structure and interesting biological properties, such as

antitumour and cardiac activity. The mild conditions of the ring-closure support the idea that the biosynthesis of the aaptamines may follow a similar course (Scheme 18).[69]



Reagents and conditions: (i): 2 N HCl, 37% HCHO, 100 °C, 45 min, then r.t., 12 h, 65%; *(ii)*: NH_3, Na, THF, 61%; *(iii)*: 1. 1% KOH, $K_2S_2O_8$, r.t., 2 h; 2. HCl, 49% (**96**), 6%(**97**).

Scheme 18

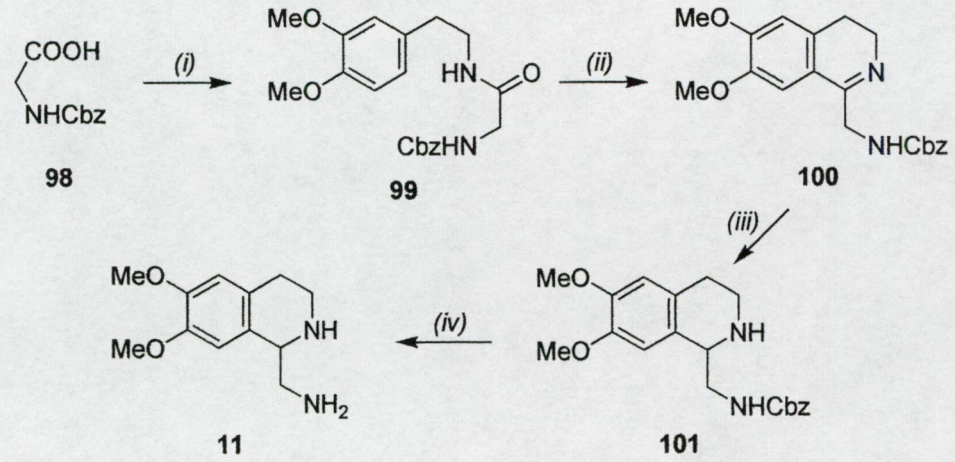
3. RESULTS AND DISCUSSION

During my experimental work, tetrahydroisoquinoline diamines and hydrazino alcohols were prepared. By ring-closures of these difunctional compounds, isoquinoline-condensed, saturated 1,3- and 1,2,3-heterocycles were produced and their conformational and ring-chain tautomeric equilibria were investigated.

3.1. Synthesis of difunctional compounds

3.1.1. Synthesis of tetrahydroisoquinoline diamines

For the preparation of 1-(aminomethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **11**, the synthetic method using an *N*-protected amino acid as starting material was chosen. The protecting group was the carbobenzyloxy (Cbz) group, which is a protecting group often used in peptide chemistry. The *N*-Cbz-glycine **98** and homoveratrylamine were coupled via the mixed anhydride method. BISCHLER-NAPIERALSKI ring-closure of carboxamide **99** resulted in dihydroisoquinoline **100**, which was reduced with $NaBH_4$ to yield tetrahydroisoquinoline **101**. **101** Was deprotected by treatment with 33% HBr in acetic acid (Scheme 19).[I]

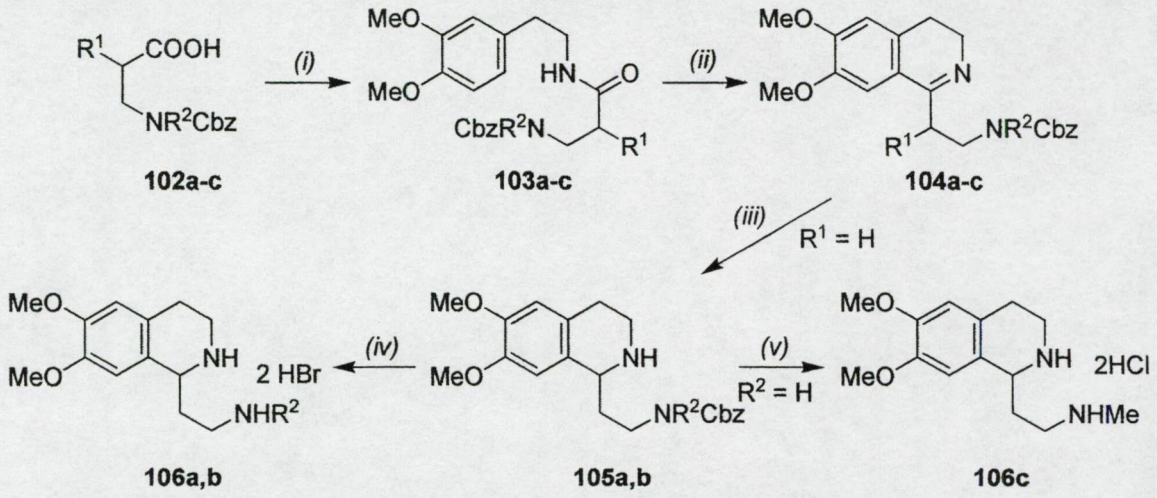


Reagents and conditions: (i): 1. ClCOOEt, Et_3N, toluene, -10 °C, 5 min.; 2. homoveratrylamine, CH_2Cl_2, 0 °C, then reflux. 5 min., 62%; *(ii)*: $POCl_3$, $CHCl_3$, reflux, 3 h, 71%; *(iii)*: $NaBH_4$, MeOH, 0 °C, 3h, then r.t., 3 h, 83%; *(iv)*: 1. HBr, AcOH, r.t., 30 min.; 2. NaOH, 78% (1+2).

Scheme 19

The 1-(2′-aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines **106a-e** were prepared in five steps, similarly to the 1-(aminomethyl)-substituted analogues, starting from the corresponding *N*-Cbz-protected β-alanines **102a-c** and homoveratrylamine. β-Alanine derivatives **102b** and **102c** were obtained by transformations of ethyl 3-anilinopropanoate[70] and

ethyl 3-amino-2-methyl-propanoate[71], respectively. Reduction of urethane **105a** with $LiAlH_4$ produced the *N*-methyl-substituted diamine **106c** (Scheme 20).



102a-c **103a-c** **104a-c**

106a,b **105a,b** **106c**

102-104: R^1, R^2 = H: **a**; R^1 = H, R^2 = Ph: **b**; R^1 = Me, R^2 = H: **c**; **105-106**: R^2 = H: **a**, R^2 = Ph: **b**

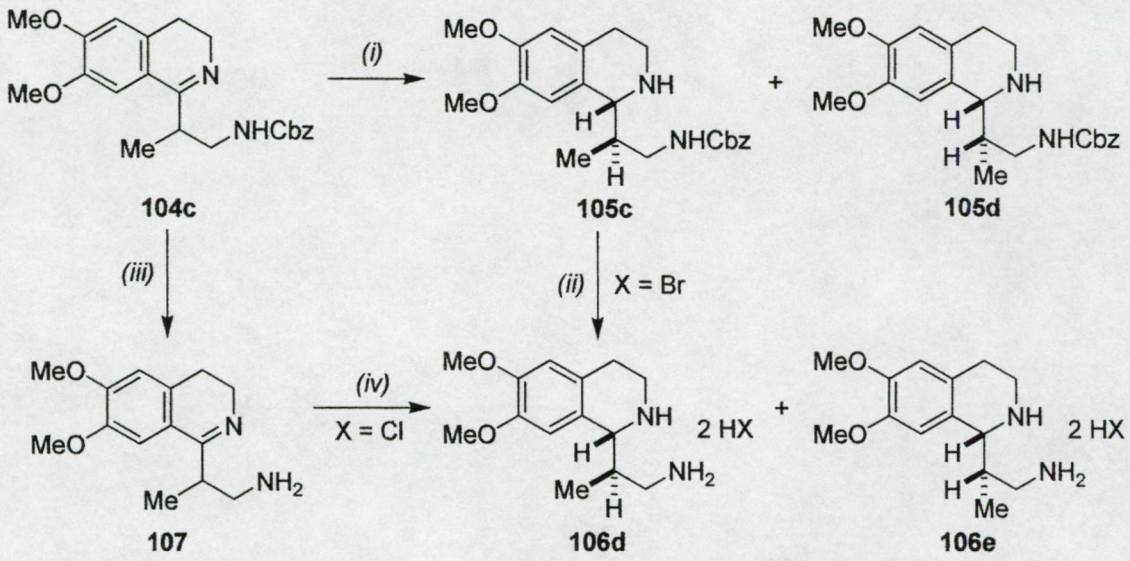
Reagents and conditions: (i): 1. ClCOOEt, Et_3N, toluene, -10 °C, 5 min.; 2. homoveratrylamine, CH_2Cl_2, 0 °C, then reflux, 5 min., 64-91%; *(ii)*: $POCl_3$, $CHCl_3$, reflux, 3 h, 65-88%; *(iii)*: $NaBH_4$, MeOH, 0 °C, 3 h, then r.t., 3 h, 82% (**105a**), 94% (**105b**); *(iv)*: HBr, AcOH, r.t., 30 min., 74% (**106a**), 78% (**106b**); *(v)*: 1. $LiAlH_4$, THF, reflux, 3 h; 2. HCl, 83% (1+2).

Scheme 20

In the transformations of dihydroisoquinoline **104c**, the reducing agent applied and the sequence of the reduction and deprotection steps proved to have marked effects on the formation of the possible diamine diastereomers. Reduction of **104c** with $NaBH_4$ gave a 7 : 1 mixture of tetrahydroisoquinoline diastereomers **105c** and **105d**, from which **105c** could be obtained by crystallization and converted to the 1*R**,1′*R** diamine diastereomer **106d**.[#] Catalytic hydrogenation of the deprotected dihydroisoquinoline **107** in the presence of Pd/C as catalyst resulted in a 1 : 10 mixture of the 1*R**,1′*R** (base of **106d**) and 1*R**,1′*S** (base of **106e**) diamine diastereomers, from which **106e** could be isolated by fractional crystallization of the dihydrochloride salt (Scheme 21).[II]

Reduction of **107** with $NaBH_4$ led to a 3 : 2 mixture of the 1*R**,1′*R** (**106d**) and 1*R**,1′*S** (**106e**) diamine diastereomers, while these isomers were formed in 1 : 1 ratio when **104c** was hydrogenated under the same conditions as applied in the catalytic reduction of **107**. The diastereomeric ratios for **105c**/**105d** and **106d**/**106e** were determined from the ^1H NMR spectra by integration of the well-separated 1′-Me doublets. The relative configurations of **106d** and **106e** were deduced from their ring-closed derivatives (see page 44).

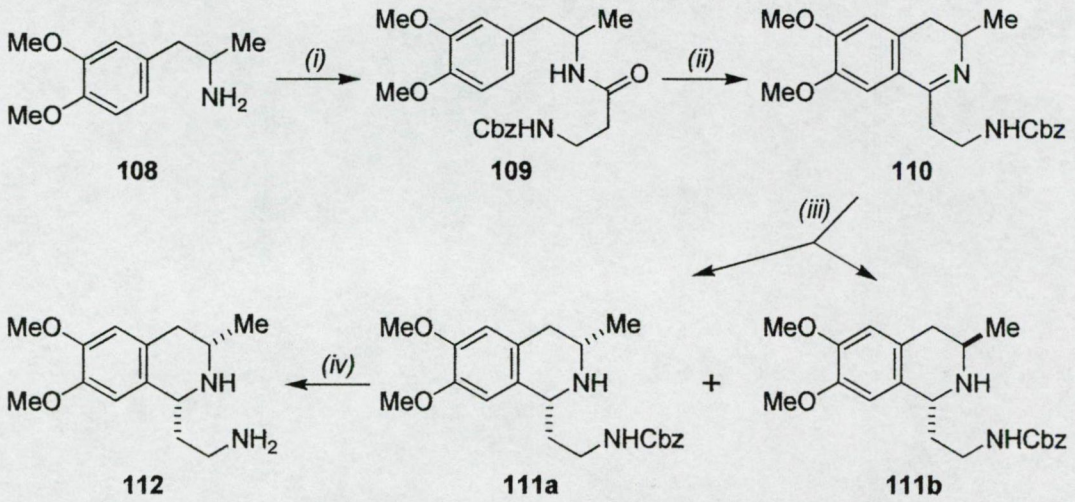
[#] During my PhD work, racemic compounds were prepared. Notations *R** and *S** refer to the relative configurations of the asymmetry centres. (IUPAC Rule R-7.2.2).



Reagents and conditions: (i): $NaBH_4$, MeOH, 0 °C, 3 h, then r.t., 3 h, **105c** : **105d** = 7 : 1, 73% (**105c**); *(ii)*: HBr, AcOH, r.t., 30 min., 69%; *(iii)*: 1. HBr, AcOH, r.t., 30 min.; 2. NaOH, 93% (1+2); *(iv)*: 1. Pd/C, H_2, MeOH, r.t., **106d** : **106e** = 1 : 10; 2. HCl, 69 % (1+2).

Scheme 21

The considerable diastereoselectivity observed in the reductions of **104c** and **107** can be rationalized by the steric effects of the methyl or Cbz groups in the dihydroisoquinolines **104c** and **107**, which are somewhat restricted conformationally by intramolecular hydrogen-bonds. The attack by hydride ions or hydrogen-bonds occurred from the sterically less hindered side of the molecule. However, the opposite diastereoselectivity observed in the reduction of **107**, depending on the reducing agent, demands further explanation.[II]



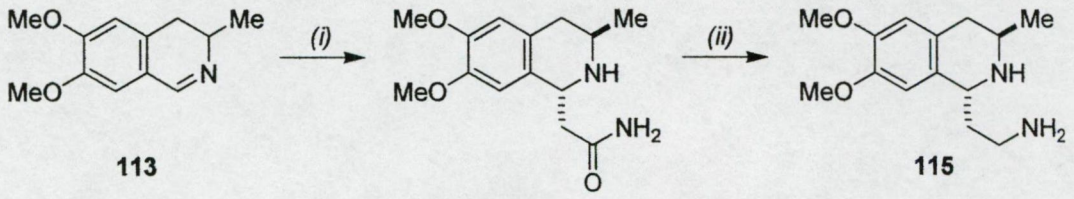
Reagents and conditions: (i): ClCOOEt, N-Cbz-β-alanine, Et_3N, toluene, -10 °C, then reflux, 5 min., 84%; *(ii)*: $POCl_3$, $CHCl_3$, reflux, 3 h, 78%; *(iii)*: $NaBH_4$, MeOH, 0 °C, 3 h, then r.t., 3 h, **111a** : **111b** = 12 : 1, 82% (**111a**); *(iv)*: 1. HBr, AcOH, r.t., 30 min.; 2. NaOH, 74% (1+2).

Scheme 22

The 3-methyl-substituted tetrahydroisoquinoline diamine diastereomers **112** and **115** were prepared by different synthetic pathways. (1*R**,3*S**)-1-(2′-Aminoethyl)-6,7-dimethoxy-3-

methyl-1,2,3,4-tetrahydroisoquinoline (**112**) was obtained by applying a procedure analogous to that used for the synthesis of **106d**. In the $NaBH_4$ reduction of dihydroisoquinoline **110**, obtained in two steps from *N*-protected β-alanine and α-methylhomoveratrylamine (**108**), a 12 : 1 mixture of tetrahydroisoquinoline isomers (1*R**,3*S**)-**111a** and (1*R**,3*R**)-**111b** was formed, from which **111a** was obtained by crystallization and was converted into the pure (1*R**,3*S**) diamine diastereomer **112** by removal of the Cbz group (Scheme 22). The *cis* selectivity of the reduction can be rationalized by the steric effect of the 3-methyl group, which directs the hydride attack to the sterically less hindered side, resulting in **111a** as the main product.[72-74] The relative configuration (1*R**,3*S**) of **112** was deduced from the NOE data on H-1 and H-3.

The (1*R**,3*R**) diamine diastereomer **115** was prepared by $LiAlH_4$ reduction of (1*R**,3*R**)-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-acetamide (**114**), which was obtained in a highly diastereoselective two-step procedure[72,73] (monoethyl malonate addition and subsequent amidation) from 3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**113**) (Scheme 23).[IV]

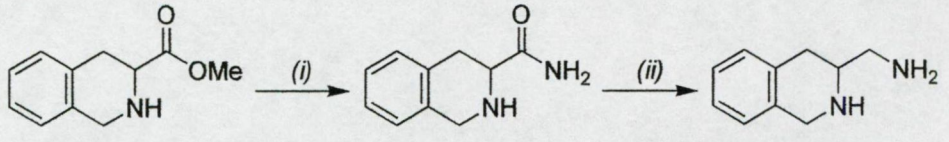


113 **114** **115**

Reagents and conditions: (i): see ref. 73; *(ii)*:$LiAlH_4$, THF, reflux, 7 h, 82%.

Scheme 23

The starting compound for the preparation of 3-aminomethyl-1,2,3,4-tetrahydroisoquinoline (**13**) was the aminoester **116**, easily available in two steps starting from DL-phenylalanine.[75] Instead of the previously reported amidation method[76], the ester **116** was converted to the amide **117** by using methanolic NH_3 solution. The carboxamide **117** was reduced to the corresponding tetrahydroisoquinoline diamine **13** with $LiAlH_4$ (Scheme 24).[I]



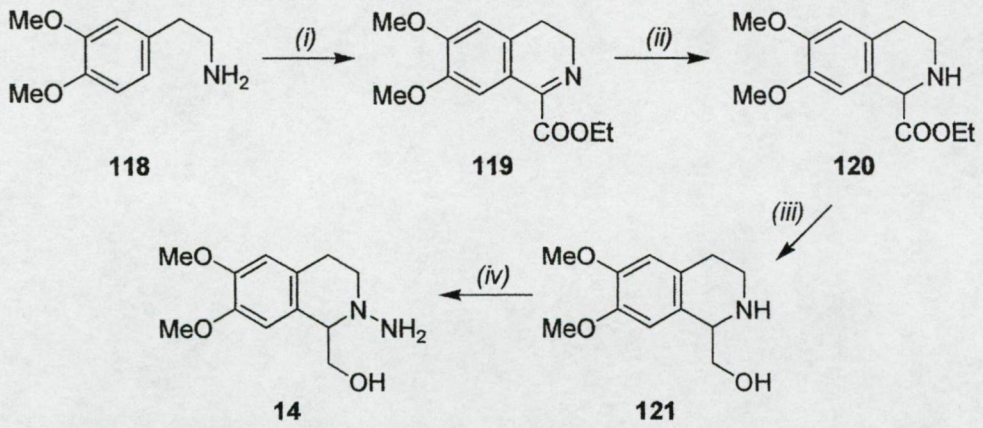
116 **117** **13**

Reagents and conditions: (i): NH_3, MeOH, r.t., 14 d, 82%; *(ii)*: $LiAlH_4$, THF, reflux, 3 h, 78%.

Scheme 24

3.1.2. Synthesis of tetrahydroisoquinoline hydrazino alcohols

Regioisomeric tetrahydroisoquinoline hydrazino alcohols (**14** and **124a,b**) were synthetized from the corresponding amino alcohol derivatives (**121** and **123a,b**) by using the two-step procedure (*N*-nitrosation and subsequent $LiAlH_4$ reduction) usually applied for the preparation of *N*-substituted hydrazines or hydrazino alcohols from secondary amines or amino alcohols, respectively (Schemes 25 and 26).[77,VIII]



118 **119** **120** **14** **121**

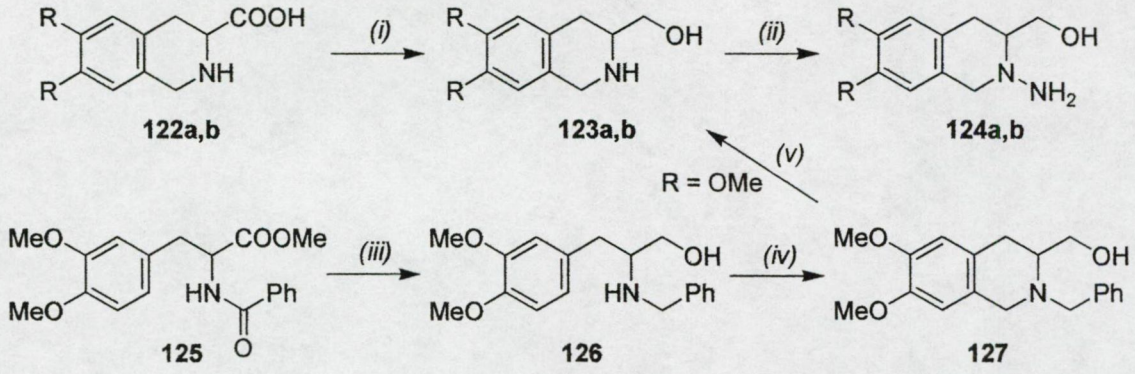
Reagents and conditions: (i): 1. $(COOEt)_2$, 140 °C, 6 h; 2. $POCl_3$, PhMe, EtOH, reflux, 3.5 h, 81%; *(ii)*: Pt/C, H_2, EtOH, r.t., 1 atm, 6 h, 82%; *(iii)*: $LiAlH_4$, THF, reflux, 3 h, 66%; *(iv)*: 1. $NaNO_2$, AcOH, H_2O, r.t., 8 h; 2. $LiAlH_4$, THF, r.t., 2 h, 52%.

Scheme 25

With regard to its natural occurrence, a great number of procedures have been developed for the synthesis of the tetrahydroisoquinoline amino alcohol derivative calycotomine (**121**),[78] which was obtained by $LiAlH_4$ reduction of the corresponding amino ester (**120**). Compound **120** was prepared by a three-step process starting from homoveratrylamine (**118**) (Scheme 25).[79,80]

The amino alcohols **123a,b** necessary for the linearly fused model compounds were synthetized by $LiAlH_4$ reduction of the corresponding 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (TIC: **122a**, and 6,7-diMeO-TIC: **122b**) (Scheme 26).[81,82]

The long hydrolysis step of **125** towards 2-amino-3-(3,4-dimethoxyphenyl)propanoic acid,[82] an intermediate of **122b**, proved to be a tedious laboratory process on a 0.1 mol scale. Accordingly, an alternative procedure,[83] based on a change in the sequence of the transformation of the functional groups of **125**, was applied for the synthesis of larger quantities of **123b**. $LiAlH_4$ reduction of **125** resulted in *N*-benzyl amino alcohol **126**, which was converted to the corresponding tetrahydroisoquinoline derivative **127** by PICTET-SPENGLER cyclization with formaldehyde. Removal of the benzyl group of **127** by catalytic hydrogenation in the presence of Pd/C led to 6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinylmethanol (**123b**) (Scheme 26).[V]



R = H: **a**; R = MeO: **b**

Reagents and conditions: (i): $LiAlH_4$, THF, reflux, 8 h, 51% (**123b**); *(ii)*: 1. $NaNO_2$, AcOH, H_2O, r.t., 8 h; 2. $LiAlH_4$, THF, r.t., 2 h, 45% (**124a**), 67% (**124b**); *(iii)*: $LiAlH_4$, THF, reflux, 5 h, 78%; *(iv)*: CH_2O, HCl, H_2O, reflux, 6 h, 92%; *(v)*: 10% Pd/C, H_2, MeOH, 30 bar, 40 °C, 30 h, ~100%.

Scheme 26

3.2. *Transformations of difunctional compounds*

3.2.1. Ring-closures with aldehydes. Ring-chain tautomerism

3-Aryl-substituted imidazo[5,1-*a*]- and -[1,5-*b*]isoquinolines

Ring-chain tautomerism, the intramolecular reversible addition of a hydroxy, mercapto or amino group to a C=N double bond, is a characteristic phenomenon for saturated, *N*-unsubstituted, five- and six-membered 1,3-*X*,*N* heterocycles (*X* = *O*, *S*, *N*R), which is often exploited advantageously in different areas of organic synthesis, and also in physical, medicinal and peptide chemistry.[84,85] Substituent effects influencing the ring-chain tautomeric process have been thoroughly studied in recent decades. For the tautomeric equilibria of oxazolidines and tetrahydro-1,3-oxazines bearing a substituted phenyl group at position 2, a linear HAMMETT-type correlation was found between the log *K* (*K* = [ring]/[chain]) values of the equilibria and the electronic character (σ^+) of the substituents X on the 2-phenyl group (Eq. 1), in both the liquid and the gas phase. The value of ρ in Eq. 1 was found to be characteristic of the ring system and dependent on the temperature and the nature of the solvent.

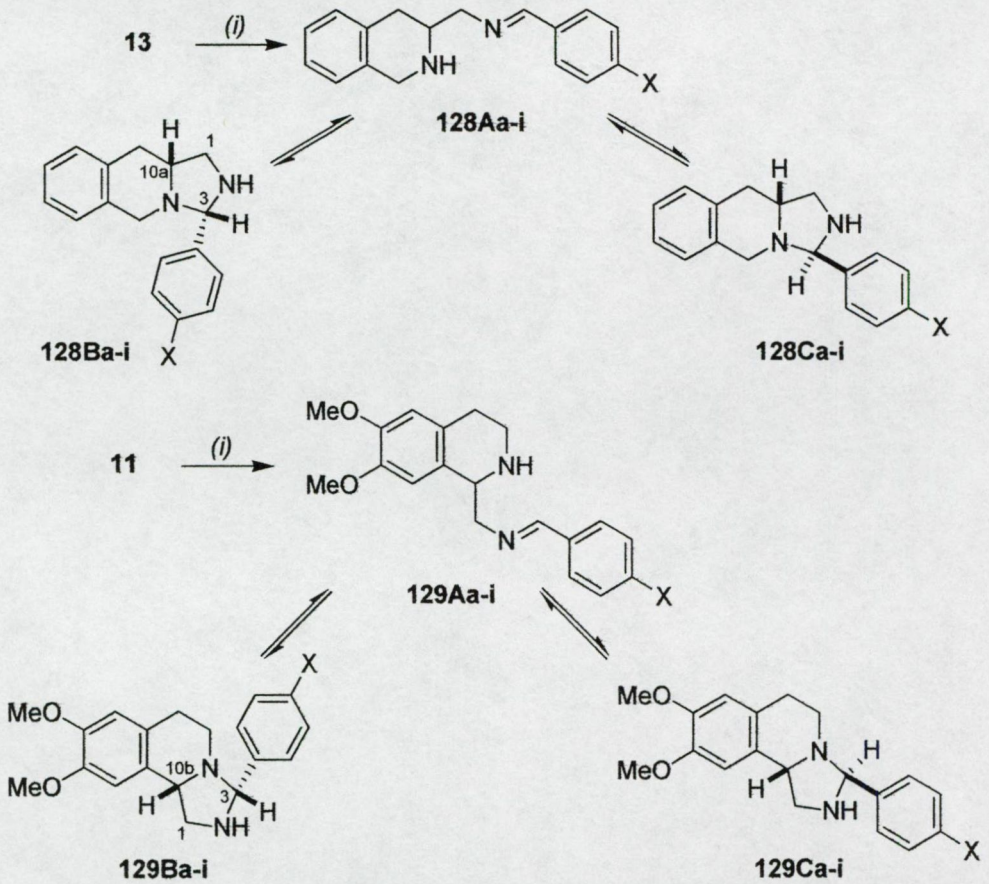
$$\log K_X = \rho\sigma^+ + \log K_{X=H} \qquad \text{(Eq. 1)}$$

Recent studies on 2-aryl-substituted imidazolidines,[86,87] hexahydropyrimidines,[88-90] 1,2,3,4-tetrahydroquinazolines[91,92] and perhydroquinazolines[93] concluded that, similarly to their 1,3-*O*,*N* analogues, the ring-chain tautomeric equilibria of these compounds could also be

characterized by Eq. 1. Complex 1,3-*N*,*N*-heterocyclic tautomeric mixtures containing regioisomeric open and/or diastereomeric cyclic forms could likewise be expressed by Eq. 1. For *N*-substituted 2-aryl-1,3-*N*,*N* heterocycles, the tautomeric process and the values of ρ and log $K_{X=H}$ in Eq. 1 were found to be dependent on the steric and electronic characters of the substituent on the nitrogen. In contrast with the 1,3-*O*,*N* analogues, the value of ρ proved not to be characteristic of the 1,3-*N*,*N* ring system.[85]

As a continuation of previous studies on five- and six-membered 1,3-*N*,*N* heterocycles, our aim was to investigate the effects of the substituents and the position of the annelated ring on the ring-chain tautomeric character of some 2-aryl-substituted imidazolidine and pyrimidine derivatives.

Through the condensations of diamines **11** and **13** with equivalent amounts of nine aromatic aldehydes, crystalline products (**128a-i** and **129a-i**) were obtained. The ^{1}H NMR spectra of **128a-i** and **129a-i** revealed that all of these compounds participated in three-component ring-chain tautomeric equilibria, involving C-3 epimeric imidazoisoquinolines (**B** and **C**) and the corresponding SCHIFF bases (**A**) (Scheme 27).



X = NO_2: **a**; CF_3: **b**; Br: **c**; Cl: **d**; H: **e**; F: **f**; Me: **g**; OMe: **h**; NMe_2: **i**

Reagents and conditions: *(i)*: CHO-C_6H_4-X, abs. MeOH, r.t., 1 h, 68-95%.

Scheme 27

After the attainment of equilibrium, the spectra of compounds **128a-i** or **129a-i** contained well-separated singlets resonating from the azomethine group at 8.31-8.46 ppm or 8.23-8.44 ppm and the two N-C*H*Ar-NH hydrogens in the region 4.11-4.63 or 4.22-4.92 ppm. The proportions K_X of the chain (**A**) and diastereomeric ring forms (**B** and **C**) participating in the tautomeric equilibria **128a-i** and **129a-i** were determined by integration of the well-separated N=C*H*Ar (chain) and N-C*H*Ar-NH (ring) proton singlets in the ^{1}H NMR spectra (Table 1). The NOESY spectra revealed that the arrangements of the H-3 and the hydrogen at the annelation (H-an) (H-10a for **128** and H-10b for **129**) in the major ring forms were opposite for the linearly and the angularly condensed imidazoisoquinolines: *cis* (**128B**) and *trans* (**129C**), respectively. The configuration of the azomethine double bond was found to be *E*.

Table 1. Proportions (%) of tautomeric forms in tautomeric equilibria for compounds **128a-i** and **129a-i** ($CDCl_3$, 300 K)

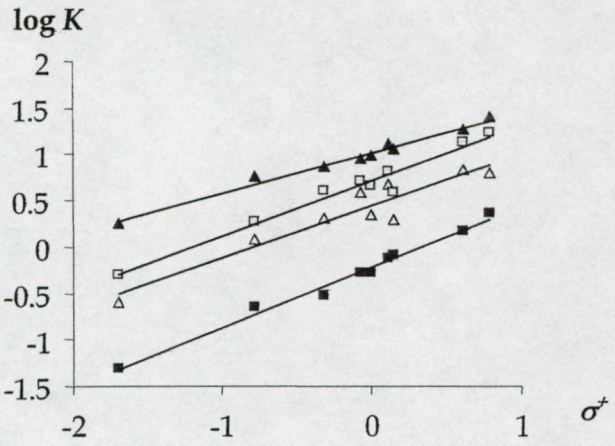
Compd	X	σ^+	**128A**	**128B**	**128C**	**129A**	**129B**	**129C**
a	*p*NO_2	0.79	3.4	88.7	7.9	4.1	25.8	70.1
b	*p*CF_3	0.612	4.8	88.2	7.0	4.7	32.0	63.3
c	*p*Br	0.15	7.6	86.1	6.3	14.7	28.9	56.4
d	*p*Cl	0.114	6.9	88.0	5.1	8.1	38.1	53.8
e	H	0	9.0	86.3	4.7	12.8	28.1	59.1
f	*p*F	-0.073	9.6	85.4	5.0	9.9	38.6	51.5
g	*p*Me	-0.311	11.6	85.0	3.4	14.3	28.9	56.8
h	*p*MeO	-0.778	14.3	82.5	3.2	24.3	29.5	46.2
i	*p*NMe_2	-1.7	34.6	63.7	1.7	57.0	14.6	28.4

When Eq. 1 was applied to the log K_X values of **128** and **129**, good linear correlations were obtained *vs* the HAMMETT-BROWN parameter σ^+ of the substituent *X* on the 4-phenyl group, for both the *cis*-chain and the *trans*-chain equilibria (Fig. 5 and Table 2).

Table 2. Linear regression data on the equilibria of **128** and **129**

Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a] (log $K_{X=H}$)	Correlation coefficient
128A ⇌ **128B**	9	0.44(2)	1.02(5)	0.9821
128A ⇌ **128C**	9	0.65(4)	0.22(1)	0.9846
129A ⇌ **129B**	9	0.56(8)	0.44(7)	0.9025
129A ⇌ **129C**	9	0.60(6)	0.72(7)	0.9607

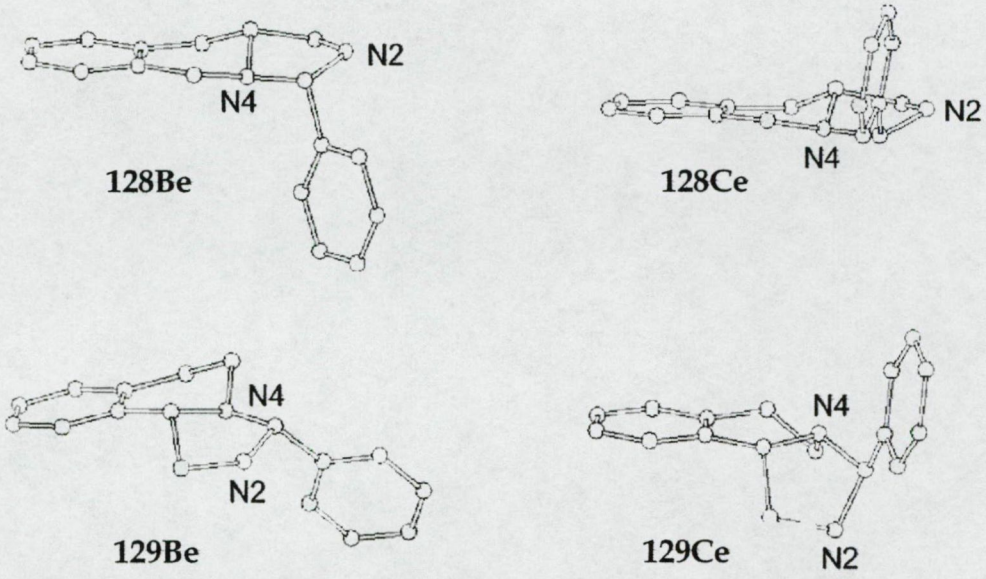
[a]Standard deviations are given in parentheses.



Plots of log K_X for **128B** (▲), **128C** (■), **129B** (△) and **129C** (□) *vs* HAMMETT-BROWN parameter σ^+

Figure 5

Because of the inversion of the nitrogen in the tetrahydroisoquinoline-fused five-membered saturated heterocycles, the stereostructure can be described by a conformational equilibrium of *cis*[1]-*trans*-*cis*[2] type. In the *trans* structure, the B/C hetero rings are *trans*-connected, with H-10b and the N-4 lone pair *trans* diaxial. In the two other configurations, the heterorings are *cis*-connected, where in the *cis*[1] conformation C-1 is in the inside, while in the *cis*[2] conformation C-1 is in the outside position.[94]



Final predominant minimum energy molecular structures for **128Be**, **128Ce**, **129Be** and **129Ce**, obtained by using *ab initio* HF/3-21G* calculations

Figure 6

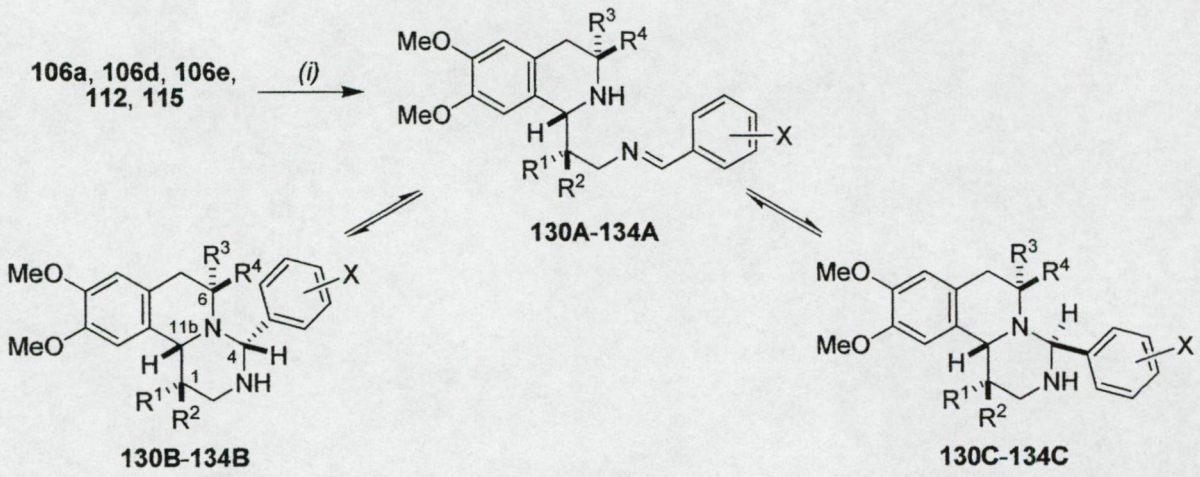
The conformational analysis of the 3-phenyl-substituted imidazo[5,1-*a*]- and -[1,5-*b*]-isoquinolines (**128e** and **129e**) was based on the NOESY spectra and *ab initio* calculations. Independently of the C-3 configuration, both the major and the minor isomers of the linearly-fused imidazoisoquinolines (**128Be** and **128Ce**) had a *trans* B/C ring connection. The conformation of the imidazo[5,1-*a*]isoquinoline was found to be dependent on the C-3 configuration: a *trans* B/C ring connection was found for the minor isomer **129Be**, while the major ring form **129Ce** had a B/C ring connection of *cis*[1] type (Fig. 6).

The relative configuration of the cyclic tautomer exerts only a small influence on the values of ρ and the intercept (log $K_{X=H}$) for the equilibria of the angularly condensed compounds (**129**), whereas considerable differences in the values of ρ and log $K_{X=H}$ were found for the *cis*-chain (**128B** $\rightleftharpoons$ **128A**) and *trans*-chain (**128C** $\rightleftharpoons$ **128A**) equilibria of the linear imidazoisoquinolines. For the latter compounds, *X*-substituent-dependent hyperconjugative interactions were observed between the nitrogen lone pair and the C-3-attached antibonding orbitals. This anomeric effect is presumed to play an important role in the ring-chain tautomeric equilibria of conformationally inflexible 2-aryl-1,3-*N*,*N*-heterocycles.[1]

4-Aryl-substituted pyrimido[6,1-*a*]isoquinolines

For the investigation of the ring-chain tautomeric character of the homologue pyrimido-isoquinolines, diamines **106a**, **106d**, **106e**, **112** and **115** were condensed with equivalent amounts of *p*-nitro- and *p*-(dimethylamino)benzaldehyde to yield crystalline products (**130-134**) (Scheme 28). In the knowledge of the strong influence of the electronic effects of the aromatic substituents on the ring-chain tautomeric behaviour of 1,3-*X*,*N* heterocyclic compounds,[84,85] aromatic aldehydes were chosen according to their opposite electronic character, which favours the predominance of either the cyclic (in the case of *p*-NO_2) or the open (in the case of *p*-NMe_2) form.

The proportions of the chain (**A**) and diastereomeric ring forms (**B** and **C**) of the tautomeric equlibria of **130-134** were determined, similarly as for the imidazo-isoquinolines, from the well-separated characteristic proton singlets in the ^{1}H NMR spectra (Table 3). The ^{1}H NMR ($CDCl_3$, 300 K) spectroscopic data on the 1-unsubstituted and 1-methyl-substituted model compounds (**130-132**) revealed that, independently of the electronic character of the aromatic substituents and the presence of the methyl group at position 1, their tautomeric equilibria were shifted totally towards the cyclic forms (**B** and **C**).



Reagents and conditions: (i): XC_6H_4CHO, MeOH, r.t., 1 h, 43-85%. (For the meanings of R^1-R^4 and X, see Table 3.)

Scheme 28

The NOESY spectra unequivocally showed that the major ring forms in the tautomeric equilibria of **130-132** contain H-4 and H-11b in the *cis* position (**B**). The proportion of the minor cyclic tautomer, possessing H-4 and H-11b in the *trans* position (**C**), was found to be increased in (1*R**,11b*R**)-1-methylhexahydropyrimido[6,1-*a*]isoquinoline **132.**

6-Methyl substitution caused dramatic changes in the tautomeric ratios. For (6*S**,11b*R**)-6-methyl-substituted hexahydropyrimido[6,1-*a*]isoquinolines **133**, the tautomeric equilibrium was found to be shifted entirely towards the open tautomer (**A**), even in **133a**, which bears an electron-withdrawing *p*-nitro substituent on the aromatic ring.

The tautomeric ratios determined for (6*R**,11b*R**)-6-methyl-substituted 4-(*p*-nitrophenyl)- (**134a**) and 4-[*p*-(dimethylamino)phenyl]hexahydropyrimido[6,1-*a*]isoquinoline (**134g**) suggested that the ring-chain equilibria of these model compounds were sensitive to the electronic effects of the 4-aryl substituents (Table 3). Accordingly, a full set of 4-(*X*-phenyl)-substituted derivatives was prepared, with substituent *X* exhibiting different electronic characters (**134a-g**). In consequence of the very similar NMR spectroscopic characteristics of **134a-g**, the relative configurations of the major (**B**) and minor (**C**) ring-closed tautomers were determined only for **134a**. The proportion of the minor cyclic form (**C**) was found to be decreased to below the limit of detection in the event of strongly electron-donating 4-aryl substituents (*p*-OMe and *p*-NMe_2).

Table 3. Proportions (%) of tautomeric forms (**A, B** and **C**) in tautomeric equilibria for compounds **130-134** ($CDCl_3$, 300 K)

Comp.	R^1	R^2	R^3	R^4	X	σ^+	**A**	**B**	**C**
130a	H	H	H	H	*p*NO_2	0.79	0	92.6	7.4
130b	H	H	H	H	*p*NMe_2	-1.7	0	100	0
131a	Me	H	H	H	*p*NO_2	0.79	0	100	0
131b	Me	H	H	H	*p*NMe_2	-1.7	0	100	0
132a	H	Me	H	H	*p*NO_2	0.79	0	65.4	34.6
132b	H	Me	H	H	*p*NMe_2	-1.7	0	81.3	18.7
133a	H	H	Me	H	*p*NO_2	0.79	100	0	0
133b	H	H	Me	H	*p*NMe_2	-1.7	100	0	0
134a	H	H	H	Me	*p*NO_2	0.79	10.7	74.7	14.6
134b	H	H	H	Me	*m*Br	0.405	17.6	75.4	7.0
134c	H	H	H	Me	*p*Br	0.15	24.1	69.2	6.7
134d	H	H	H	Me	H	0	31.4	64.9	3.7
134e	H	H	H	Me	*p*Me	-0.311	40.8	57.2	2.0
134f	H	H	H	Me	*p*OMe	-0.778	54.9	45.1	0
134g	H	H	H	Me	*p*NMe_2	-1.7	79.4	20.6	0

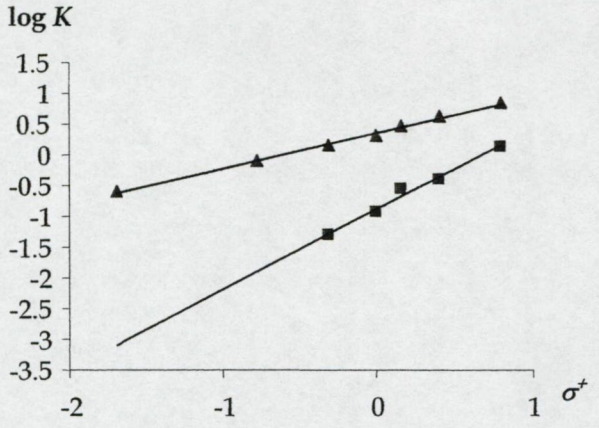
4-Aryl substituents did not change the sequence of the chemical shifts of the characteristic N-C*H*Ar-N and N=C*H*Ar protons. The azomethine double bond configuration was found to be *E*, in accordance with the NOE interaction observed between H-2 and N=C*H*.

Table 4. Linear regression data on compounds **134**

Equilibrium	No. of points	Slope[a] (ρ)	Intercept[a] (log $K_{X=H}$)	Correlation coefficient
134A ⇌ **134B**	7	0.36(5)	0.57(6)	0.995
134A ⇌ **134C**	5	1.30(9)	-0.88(6)	0.982

[a]Standard deviations are given in parentheses.

When Eq. 1 was applied to the log K_X values of **134a-g**, good linear correlations were obtained *vs* the HAMMETT-BROWN parameter σ^+ of the substituent *X* on the 4-phenyl group for both the *cis*-chain (**B-A**) and the *trans*-chain (**C-A**) equilibria (Fig. 7 and Table 4).



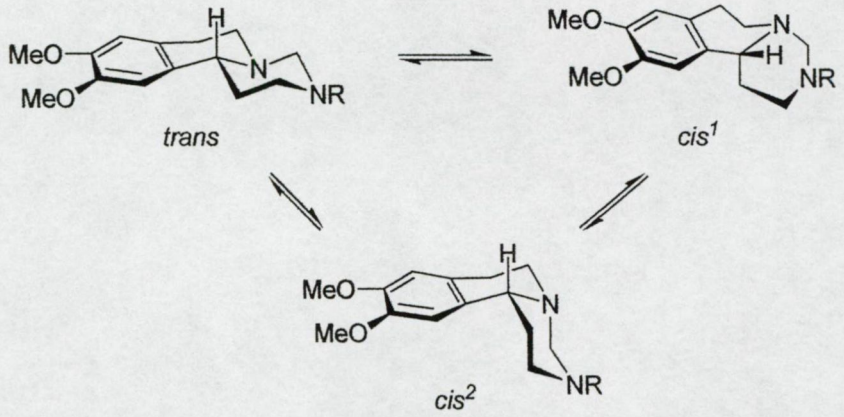
Plots of log K_X for **134B** (▲) and **134C** (■) *vs* HAMMETT-BROWN parameter σ^+

Figure 7

The data in Table 4 show that both the slope (ρ) and the intercept (log $K_{X=H}$) of the regression line were strongly influenced by the relative configuration of C-4 and C-11b. The difference in the values of ρ for the *cis*-chain (**134B**⇌**134A**) and *trans*-chain (**134C**⇌**134A**) equilibria, which reflects the difference in the sensitivities of the reactions to electron supply or withdrawal, was found to be considerably higher ($\Delta\rho$ = 0.94) than that observed for the ring-chain tautomeric equilibria of the analogous 3-aryl-hexahydroimidazo[5,1-*a*]isoquinolines ($\Delta\rho$ = 0.04).[1] The different values of ρ for the *cis*-chain (**134B**⇌**134A**) and *trans*-chain (**134C**⇌**134A**) equilibria can probably be rationalized by the different hyperconjugative (anomeric) effects[1] in **134B** and **134C**, possessing different predominant B/C ring connections.

The substantial increase in the proportions of the open tautomers for the equilibria of **133** and **134**, as compared with the tautomeric ratios for **130-132**, can be interpreted by the increased steric hindrance of the *N*-substituent caused by the 6-methyl group. Earlier data on the ring-chain tautomeric equilibria of 1,3-*N*,*N*-heterocycles indicated that the proportion of the ring-closed form decreases with increasing bulkiness of the *N*-substituent.[85]

Similarly to the tetrahydroisoquinoline-fused five-membered saturated heterocycles, the conformational equilibria of the tetrahydroisoquinoline-fused six-membered heterocycles can also be characterized as of *cis*[1]-*trans*-*cis*[2] type (Figure 8). The conformational equilibria of 1-, 2- and 4-substituted saturated 1,3-oxazino[4,3-*a*]-,[10,95] 1,2,3-oxathiazino[4,3-*a*]-[12] and 1,3,2-oxazaphosphorino[4,3-*a*]isoquinolines[13,14] have been thoroughly studied, but fewer data are available on the analogous hexahydropyrimido[6,1-*a*]isoquinolines. A slight predominance of the conformer with *trans*-connected B/C rings was found for the conformational equilibrium of the 3-methyl-substituted parent compound in $CDCl_3$.[96]

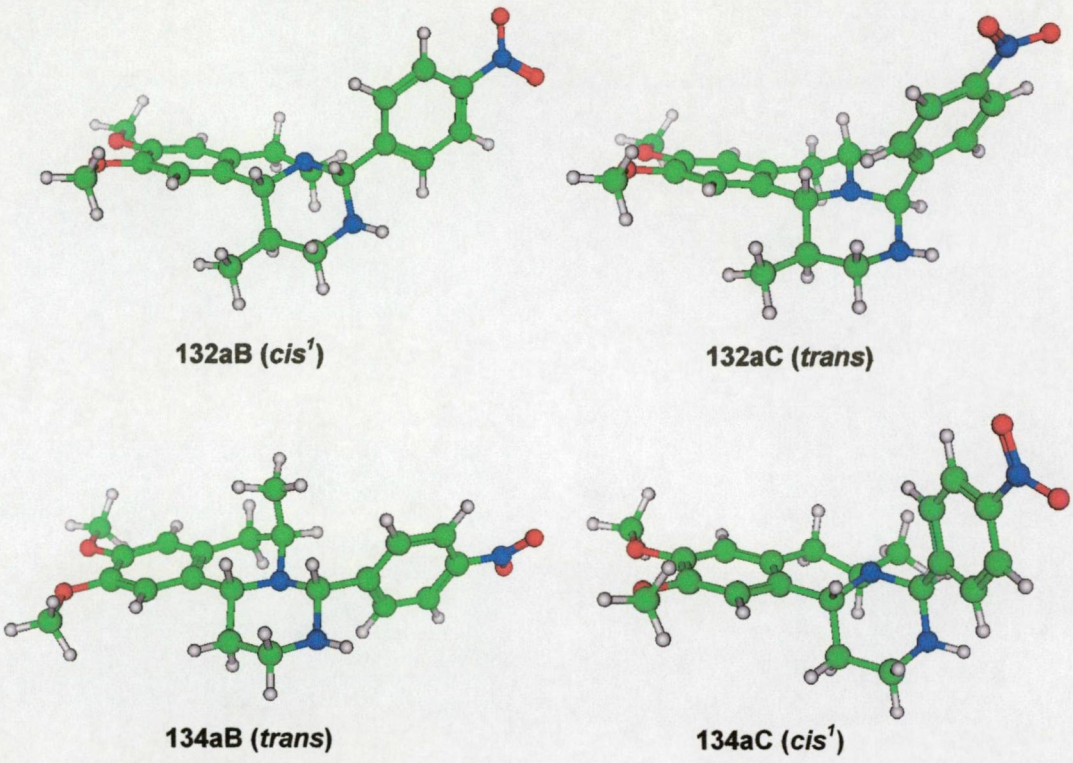


Possible steric structures of 1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]-isoquinolines

Figure 8

Conformational analysis of the prepared hexahydropyrimido[6,1-*a*]isoquinolines was performed only for the 4-(*p*-nitrophenyl)-substituted derivatives, which contain the cyclic tautomers in the highest proportions. To determine the mode of connection of the B/C rings, ^{1}H NMR spectroscopic methods were used, since the geometries of the B/C ring connections of *cis*^{1} or *cis*^{2} or *trans* type produce different patterns of cross-peaks derived from the 1,3-diaxial protons in the NOESY spectra. While the stereostructures of the major cyclic forms (**B**) of the prepared model compounds could be determined in each case (**130a-132a** and **134a**), the relatively low abundance of the minor cyclic form (**C**) meant that its conformational analysis could be performed only for **132a**.

For **130aB** and **131aB**, the NOESY spectra showed H-11b–H-6$_{ax}$, H-11b–H-4, and H-4–H-6$_{ax}$ NOE cross-peaks, which are typical for a B/C *trans*-arranged ring junction with an equatorial aromatic substituent. For **132aB**, however, the NOESY spectrum revealed H-1–H-6$_{ax}$, H-11b–H-2$_{ax}$ and H-11b–H-4 NOE cross-peaks, which unequivocally proved the *cis*^{1} connection of the B/C rings. For **132aC**, the NOESY cross-peaks for H-11b with H-2$_{ax}$, H-6$_{ax}$ and the *ortho* protons of the 4-(*p*-nitrophenyl) substituents pointed to a *trans* B/C ring junction with an *axial* aromatic substituent. The NOESY cross-peaks for the (11b*R**,6*R**)-6-methyl-substituted C-4 epimeric model compounds (**134aB** and **134aC**) could be characterized by different B/C ring junctions: *trans* for **134aB** (NOESY cross-peaks: H-11b–H-2$_{ax}$, H-11b–H4 and H-4–Me-6$_{ax}$), and *equatorial* and *cis*^{1} for **134aC** (NOESY cross-peaks: H-11b–H-2$_{ax}$ and H-4–Me-6$_{ax}$) with an *axial* 4-(*p*-nitrophenyl) substituent.



Stereoviews of typical minimum-energy structures for **132aB** and **132aC** and for **134aB** and **134aC**

Figure 9

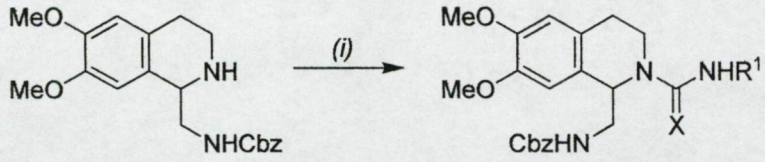
The structures of the C-4 epimers of **132a** and **134a** were confirmed by molecular modelling. Figure 9 depicts the typical minimum-energy molecular structures for **132aB** and **132aC** and for **134aB** and **134aC**. The steric hindrance between H-11 and the 1-methyl group (for **132aB**), or between the 6-methyl and 4-(*p*-nitrophenyl) groups (for **134aC**), makes the predominant conformation with *trans*-arranged B/C rings unfavourable and shifts the conformational equilibrium towards the *cis*[1] structure.[IV]

3.2.2. Tetrahydroisoquinoline diamine derivatives with multidrug resistance reversal activity

The treatment of metastatic cancer is often unsuccessful, due to the development of multidrug resistance (MDR) of the tumour cells. Multidrug-resistant tumours display cross-resistance to many classes of chemotherapeutic agents that were never part of their treatment. A number of studies have demonstrated that a wide range of structurally and functionally unrelated compounds (*e.g.* calcium channel blockers, calmodulin inhibitors, antimalarial agents and cyclosporines), are able to reverse MDR by modulation of a plasma membrane-bound protein (P-gp) or MDR protein (MRP1). However, since these first-generation MDR inhibitors are active only at high concentrations, they have proved to be of only limited relevance in

clinical practice. In recent years, enormous efforts have been made to find new natural or synthetic compounds with MDR reversal activity.[97-100]

In view of the great therapeutic importance, our aim was to find new compounds with MDR reversal activity. In cooperation with the group of Prof. de Witte at the University of Leuven, *ca* 150 compounds prepared in recent years at the Institute of Pharmaceutical Chemistry were tested for MDR reversal effect. Some hits were found among 1,2-disubstituted tetrahydroisoquinoline derivatives containing *N*-thiocarbamoyl moieties, and various tetrahydroisoquinoline diamine derivatives were prepared to refine the structure-activity relationships.



101 **135a-k**

Reagents and conditions: *(i)*: R^1NCX, toluene, reflux, 1 h, 64-86%.

Scheme 29

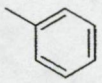
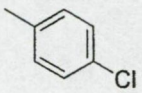
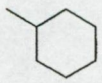
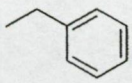
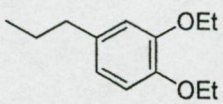
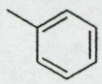
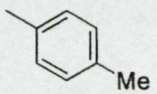
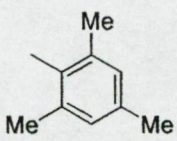
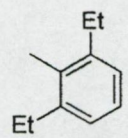
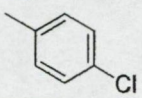
The target compounds were synthetized by using *N*-substitution reactions of **101**, an intermediate of the synthesis toward tetrahydroisoquinoline diamine **11**. When **101** was reacted with isocyanates or isothiocyanates, the corresponding urea or thiourea derivatives were formed in good yields (Scheme 29).

The compounds were assayed as P-gp inhibitors in a fluorescence microtitre plate assay, using a standard functional assay with rhodamine 6G as a fluorescent probe on MCF-7/Adr cells to assess MDR activity. Verapamil, a well-known MDR modulating agent, was used as a positive control.

The extent of rhodamine 6G accumulation observed in the presence of the individual test compounds (40 μM) was expressed relative to the accumulation observed with untreated MCF-7/Ard cells. The accumulation factor (AF) was calculated as the mean of 3 independent experiments. For the compounds that displayed an AF > 3.0 (approximately the AF of verapamil), concentration-response curves were constructed and the AC_{50} values (the concentrations of the test compounds eliciting 50% of their maximum effect on rhodamine 6G accumulation) were determined. Cytotoxicity was investigated on HeLa (human cervix carcinoma) cells, using an antiproliferative assay. Concentration-response curves were constructed and the IC_{50} values (the concentrations of the test compounds inhibiting 50% of cell proliferation) were determined (Table 5). Six compounds (**135a-b, 135d, 135g, 135i** and **135j**)

were found to have an AF > 3.0, which indicates that they are at least as effective as verapamil as inhibitors of P-gp.

Table 5. Accumulation factor (AF), IC_{50} and EC_{50} values of the investigated tetrahydroisoquinoline derivatives and verapamil

	R^1	X	AF	AC_{50} (μM)	IC_{50} (μM)	Ratio (IC_{50}/AC_{50})
135a		O	8.69±0.94	7.3±0.9	14.0±3.9	1.9
135b		O	7.04±0.21	8.0±0.18	>80	>10
135c		S	2.49±0.11	-	-	-
135d		S	3.67±0.16	8.0±0.18	>80	>10
135e		S	2.72±0.06	-	-	-
135f		S	1.73±0.05	-	-	-
135g		S	3.73±0.28	8.1±0.5	7.7±0.12	0.9
135h		S	1.52±0.08	-	-	-
135i		S	8.22±0.52	3.9±0.08	7.5±0.48	1.9
135j		S	5.69±0.57	3.8±0.4	13.3±2.8	3.5
135k		S	1.39±0.04	-	-	-
Verapamil			3.11±0.11	24.0±4.3	>80	>3.3

All compounds were found to have an AC_{50} significantly lower than that of verapamil. The respective IC_{50}/AC_{50} ratios were also calculated: the larger this ratio, the less the compound induces a cytotoxic effect at concentrations that are effective in inhibiting P-gp, reversing the MDR phenotype of the treated malignant cells.[III]

3.2.3. Phosphorus-containing 1,2,3- and 1,2,3,4-heterocycles

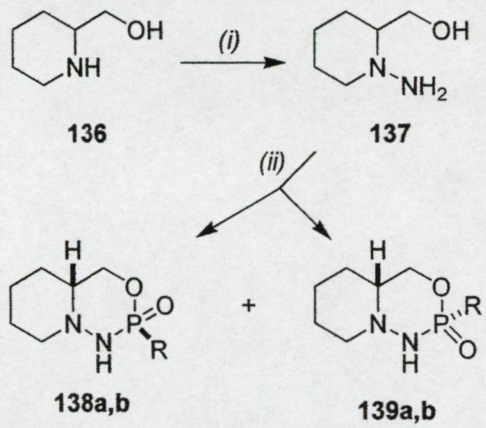
Tetrahydroisoquinoline- and piperidine-fused 1,3,4,2-oxadiazaphosphinanes

In consequence of their valuable pharmacological effects and wide-ranging possibilities for synthetic applications, considerable interest has been demonstrated in the 1,3,2-*O,N,P*-heterocycles.[VII] The 1,3,2-oxazaphosphinane ring system is found in alkylating anticancer drugs (cyclophosphamide and ifosfamide), numerous derivatives of which have been synthetized to determine their structure-activity relationships.[101,102] Compounds containing a 1,3,2-oxazaphosphinane moiety were recently reported to possess matrix metalloproteinase-inhibitory,[103,104] pesticidal[105] and antimicrobial[106] activities. Phosphorus-stabilized carbanions derived from chiral 1,3,2-oxazaphosphinane 2-oxides have been widely used in the diastereoselective formation of carbon-carbon bonds.[107,108]

In contrast with the thoroughly investigated 1,3,2-oxazaphosphinane-2-oxide derivatives, less attention has been paid to the synthesis and transformations of the corresponding 1,3,4,2-oxadiazaphosphinane-2-oxides containing another nitrogen in the heterocyclic ring.[109-113] The first representatives of this ring system were prepared with the aim of finding potential antitumour agents. However, despite the close structural analogy, cyclophosphamide-analogue 1,3,4,2-oxadiazaphosphinane-2-oxides and the homologous 1,3,4,2-oxadiazaphosphepin-2-oxides proved to exhibit very low or practically no anti-leukaemic activity[109,110] There has been only one stereochemical investigation of this ring system: 4-methyl-2-phenoxy-1,3,4,2-oxadiazaphosphinane-2-oxide proved to exist predominantly in the chair conformation, with the P=O group in an axial position.[111]

1,3,4,2-Oxadiazaphosphinane 2-oxides attached angularly or linearly to the tetrahydroisoquinoline ring were planned to be prepared in order to investigate the effects of the substituents and the configurations of the substituted atoms on the predominant conformations of the nitrogen-bridged tricyclic system. To determine the effects of the attached aromatic ring on the stereochemistry of the ring junction, syntheses of the parent piperidine-condensed derivatives were also among our aims.

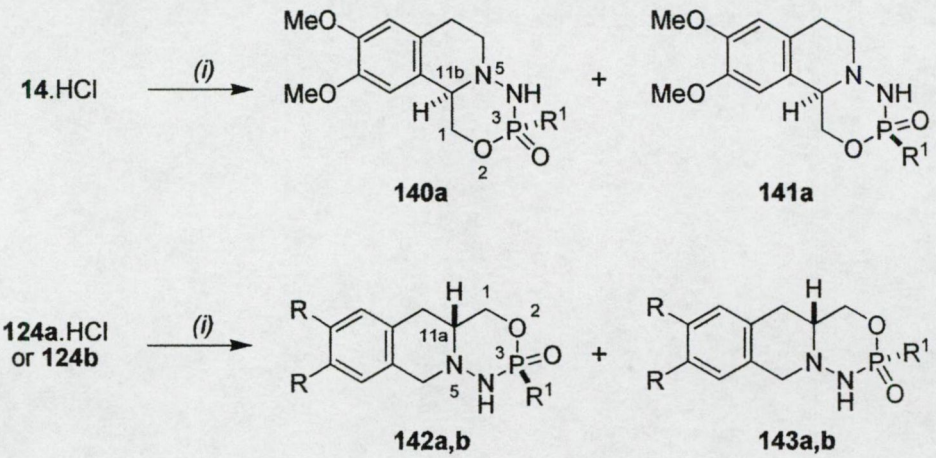
Most of the methods applied earlier for the synthesis of 1,3,4,2-oxadiazaphosphinanes were based on the ring-closures of the corresponding hydrazino alcohols with the appropriate phosphorus-containing fragments.[109,111-113] This methodology was also applied for the preparation of our target compounds.



	R	Diastereomeric ratio (**138** : **139**) in the crude product
a	Ph	21 : 79
b	OPh	50 : 50

Reagents and conditions: (i). see ref. 114.; *(ii)*: Cl_2POR, Et_3N, THF, r.t., 48 h, 34-41%.

Scheme 30



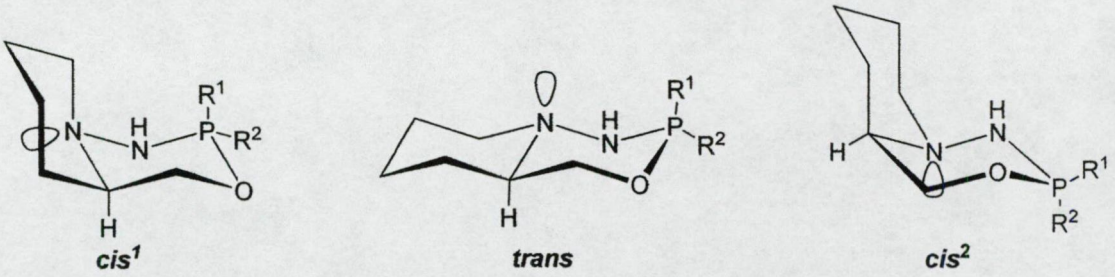
		R	R^1	Diastereomeric ratio (**140** : **141** or **142** : **143**) in the crude product
140, 141	**a**	-	Ph	48 : 52
142, 143	**a**	H	Ph	50 : 50
142, 143	**b**	OMe	Ph	~0 : ~100

Reagents and conditions: (i): Cl_2POR^1, Et_3N, THF, r.t., 48 h, 34-51%.

Scheme 31

Hydrazinoalcohols **14**, **124a,b** and **137**[114] were cyclized with phenylphosphonic dichloride and phenyl dichlorophosphate at ambient temperature in THF in the presence of Et_3N, resulting in 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*]1,3,4,2-oxadiazaphosphinine-3-oxides (**138** and **139**), 1,6,7,11b-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[5,4-*a*]isoquinoline-3-oxides (**140** and **141**) and 1,6,11,11a-tetrahydro-4*H*-1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinoline-3-oxides (**142** and **143**), which are the first representatives of these ring systems (Schemes 30 and 31). In most cases, two *P*-2 epimeric diastereomers differing in the *cis* or *trans* position of the *P*-substituent and H-an, were formed and were separated by column chromatography. A significant difference was found in the ratios of the *P*-2 epimers for **138a** and **139a**, the *trans* isomer (**139a**) being the main product, while in the ring-closure of **124b**, the minor oxadiazaphosphinane diastereomer (**142b**) could not be detected, even in the crude product.

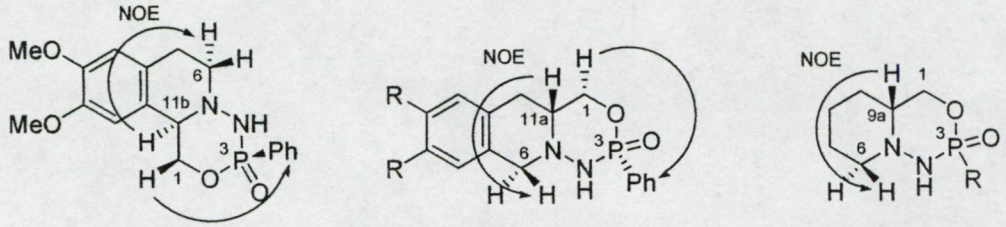
Similarly to those of nitrogen-bridged saturated bi- or polycyclic heterocycles, the stereostructures of the 1,3,4,2-oxadiazaphosphinanes prepared (**138-143**) can be described by a conformational equilibrium of *cis*[1]-*trans*-*cis*[2] type.[115] In the *trans* structure, the B/C hetero rings are *trans*-connected, with a *trans-diaxial* arrangement of the H-an and the nitrogen lone pair. In the two other configurations, the hetero rings are *cis*-connected: for the *cis*[1] conformation, C-1 is in the inside, while for the *cis*[2] conformation, C-1 is in the outside position (Fig. 10). The phosphorus-containing 1,2,3-heterocycles are prone to participate in a conformational equilibrium involving chair, twisted chair and other distorted conformations.[VII,14]



Possible ring connections of 1,6,7,8,9,9a-hexahydro-4*H*-pyrido[1,2-*d*]-[1,3,4,2]oxadiazaphosphinines

Figure 10

The stereochemistry of the model compounds was determined in two steps. First, the predominant conformation was assigned on the basis of the characteristic ^3J couplings and NOE interactions. Second, the relative configuration of the *P*-phenyl substituent was observed by using the NOEs from the *P*-phenyl group to the annelation protons (where applicable) and/or the significant differences in the chemical shifts for certain indicator nuclei.



141a **143a,b** **138a,b; 139a,b**

Detected NOEs

Figure 11

The orientation of H-an (*i.e.* H-11b for **140a** and **141a**; H-11a for **142** and **143**; and H-9a for **138** and **139**) and the protons connected to the carbons adjacent to the annelation (H-1 and H-X; H-X: H-11 for **142** and **143**, and H-9 for **138** and **139**) or the protons connected to the carbons adjacent to the nitrogen-bridge (H-6) were assigned by using the vicinal coupling constants (Table 6) and the detected NOESY cross-peaks (Fig. 11).

The data in Table 6 show that H-an for **143a,b**, **138a,b** and **139a** has two high vicinal couplings to the axial protons connected to the carbons adjacent to the annelation (H-X, *i.e.* H-11 for **142a,b** and **143a,b**; and H-9 for **138a,b** and **139a,b**), indicating that H-an is in the axial position and the hetero rings are *trans*-connected. The vicinal couplings of H-11b for **140a** and **141a** correspond to a *trans* diaxial position for H-11b and H-1_{ax}, which excludes the hetero ring connection of *cis*[2] type. The NOESY cross-peaks detected for H-11b and H-6_{ax} indicate the *trans* connection of the hetero rings for both compounds.

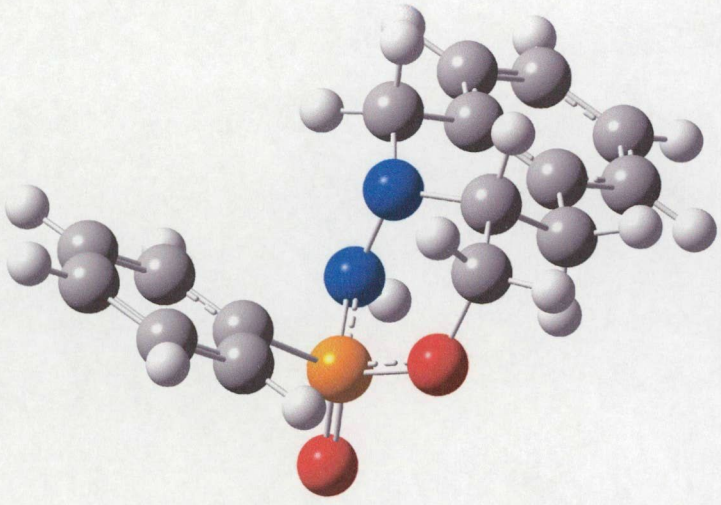
Table 6. Characteristic vicinal coupling constants (in Hz)*

Compd.	H-1_{ax}–H-an	H-1_{eq}–H-an	H-X_{ax}–H-an	H-X_{eq}–H-an	H-1_{ax}–P	H-1_{eq}–P
138a	9.8	3.3	10.1	2.8	3.5	18.9
139a	10.3	3.0	10.0	3.1	2.0	20.4
138b	10.6	3.5	10.1	3.0	1.6	19.9
139b	9.0	3.5	overlap	overlap	2.3	26.4
140a	9.3	4.3	-	-	5.3	17.1
141a	10.6	2.8	-	-	1.3	18.6
142a	4.0	2.5	11.8	5.5	3.8	20.0
143a	9.8	4.0	10.6	4.8	7.3	18.4
143b	8.2	3.8	10.3	4.8	8.1	18.1

*For the meanings of H-an and H-X, see the text.

For **142a**, the ^3J(H-1_{ax}–H-11a) and ^3J(H-1_{eq}–H-11a) values were 4.0 and 2.5 Hz, respectively, which suggest that H-an is equatorial to the oxadiazaphosphinane ring. This is

supported by the equally strong NOE from H-11a to both H-1 protons. The vicinal couplings between H-11a and protons H-11 show an axial orientation of H-11a with respect to the isoquinoline ring. These findings are in accord with two possible conformations: a *cis*[2]-connected chair-chair and a *trans*-connected chair-boat. In order to decide between these, *ab initio* molecular modelling was performed at the HF/6-31* level. The calculations revealed that conformation *cis*[2] is 5.3 kcal/mol more stable, and we therefore believe that the hetero rings are predominantly *cis*-connected (*cis*[2] conformation; Fig. 12).



Ab initio geometry obtained for **142a**

Figure 12

As concerns the orientation of the *P*-substituent, P-Ph–H-1_{ax} NOE interactions could readily be detected in **141a** and **143a,b** (Fig. 11), which indicates the axial arrangement of the *P*-phenyl group and its position *trans* to H-an (H-11b or H-11a, respectively).

P-Ph–H-1_{ax} or P-OPh–H-1_{ax} NOE interactions could not be determined unambiguously for compounds **138a** and **139a**, and the *P*-configuration was therefore deduced from the chemical shifts calculated by using the GIAO method at the HF/6-31G* level and the geometrical constraints obtained by means of NMR. It is a trend that H-1_{ax} exhibits an upfield shift in compounds containing an axial *P*-phenyl group (*i.e. trans* to H-an), due to the ring current shielding.

The comparison of the experimental and theoretical chemical shifts (Table 7) unambiguously corroborated the assignment. Unfortunately, the phenoxy derivatives (**138b** and **139b**) did not allow utilization of the shielding effect because of the flexible aromatic substituent; the stereochemical assignment is therefore based purely on the X-ray data.

Table 7. Experimental and calculated characteristic chemical shifts (in ppm) ($\delta_{TMS} = 0$, $\delta_{NH_3} = 0$)

Compd.	H-1_{ax}		H-1_{eq}	
	Exp.	Calcd.	Exp.	Calcd.
138a	4.42	3.97	4.13	3.45
139a	3.78	3.02	4.16	3.39
138b	4.23	3.69	4.17	3.18
139b	4.26	3.73	4.31	3.50
140a	4.72	4.09	4.58	3.91
141a	4.05	3.29	4.72	3.87
142a	4.44	3.27	4.32	3.48
143a	3.99	3.04	4.51	3.53
143b	3.97	3.01	4.46	3.49

The steric assignment of the *P*-2 epimers of **138** and **139**, based on the results of NMR experiments and theoretical calculations, was in accordance with the X-ray crystal structures of **139a** and **139b** (Fig. 13).[v]

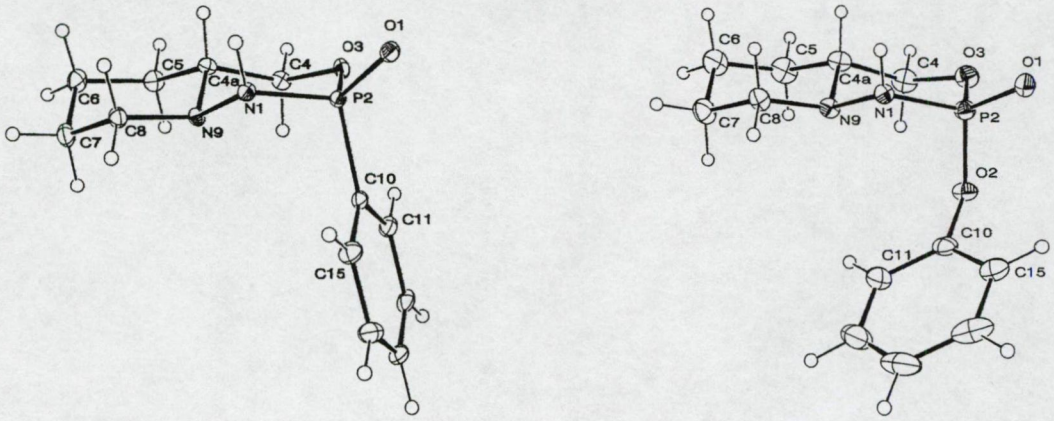
The stereochemical assignments for **138-143** are presented in Table 8.

Table 8. Stereochemical assignments for **138-143**

Compd.	Steric position of H-an and the *P*-substituent	Stereochemistry of the junction of the hetero rings	Oxadiazaphosphinane ring conformation
138a	*cis*	*trans*	chair
139a	*trans*	*trans*	chair
138b	*cis*	*trans*	chair
139b	*trans*	*trans*	chair
140a	*cis*	*trans*	chair
141a	*trans*	*trans*	chair
142a	*cis*	*cis*	chair
143a	*trans*	*trans*	chair
143b	*trans*	*trans*	chair

The chair conformation found for 1,3,4,2-diazaphosphinanes angularly fused to tetrahydroisoquinoline (**140a**, **141a**) is substantially different from the steric structures of the

analogous 1,3,2-oxazaphosphino[4,3-*a*]isoquinolines, which could be characterized by distorted conformations of the 1,3,2-oxazaphosphinane ring.[14]



X-ray crystal structures of **139a** and **139b**. The thermal displacement ellipsoids are drawn at a probability level of 30%

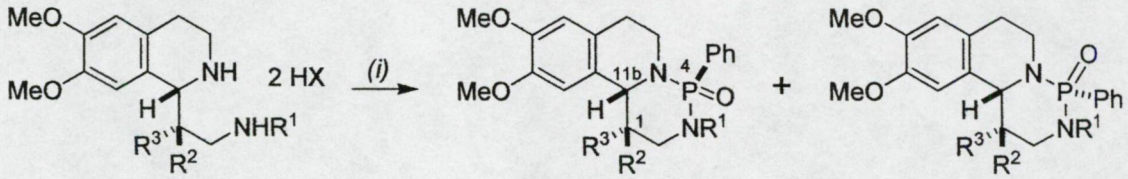
Figure 13

1,3,2-Diazaphosphino[6,1-*a*]isoquinolines

In contrast with the 1,3,2-oxazaphosphinane-2-oxides, which have been thoroughly investigated from both pharmacological and stereochemical points of view,[14,102] less attention has been paid to the synthesis and stereochemistry of the aza-analogue 1,3,2-diazaphosphinane-2-oxides. The first publications on the conformations of saturated 1,3,2-diazaphosphinane 2-oxides contained much uncertainty concerning the axial/equatorial orientation of the *P*-substituents.[116-119] The stereochemical investigations of this type of heterocyclic compounds became of considerable interest when chiral phosphoramides proved to be effective auxiliaries with which to induce stereoselective carbon-carbon or carbon-hydrogen bond-forming reactions, *e.g.* asymmetric aldol reactions,[120-122] allylations of aldehydes,[123] α-alkylations of *P*-alkyl derivatives[124] and reductions of ketones.[125] Stereochemical studies on some 1,3,2-diazaphosphinane-2-oxide model compounds led to the conclusion that, in contrast with the conformationally diverse 1,3,2-oxazaphosphinane analogues, these compounds could be characterized by chair or flattened chair conformations.[126,127]

The ring-closure reactions of diamines **106a-e** with phenylphosphonyc dichloride were accomplished by the usual literature methods,[128] to yield 1,3,2-diazaphosphino[6,1-*a*]isoquinolines (**144** and **145**), which are the first representatives of this ring system (Scheme 32). The *N*-substituents proved to have significant effects on the ratios of the diastereomers formed: in the case of the *N*-unsubstituted diamines (**106a,d,e**) the diastereomers of type **144**, containing a 4-phenyl group and H-11b in the *cis* position, were the major isomers, while the *N*-phenyl-

and *N*-methyl-substituted diamines (**106b,c**) gave isomers of type **145** as the main products. In the ring-closure of the 1*R**,1′*R** 1′-methyl-substituted diamine diastereomer (**106d**), the minor diazaphosphinane isomer of type **145** could not be detected, even in the crude product.



106a-e **144a-e** **145a-e**

	R1	R2	R3	Diastereomeric ratio (**144** : **145**) in the crude product
a	H	H	H	56 : 44
b	Ph	H	H	29 : 71
c	Me	H	H	27 : 73
d	H	Me	H	~100 : ~0
e	H	H	Me	57 : 43

Reagents and conditions: (i): $PhPOCl_2$, Et_3N, CH_2Cl_2, 6-10 °C, 24 h, 25-49%.

Scheme 32

For compound **145**, a systematic increase in the chemical shifts of H-2_{ax} is detected as compared with compounds **144** (Table 9), which is due to the shielding effect of the oxygen in the 1,3-diaxial position relative to H-2_{ax} (H-2_{ax} is assigned because of the NOE interaction with H-11b.) The NOE interactions between the *ortho*-hydrogens of the phenyl group on the phosphorus and H-11b can be detected in each case in the series **144**. These findings unequivocally show that H-11b and the phenyl substituent on the phosphorus are located on the same side of the best plane of the diazaphosphinane ring in **144**. The assignment of the relative configuration is supported by the ^{31}P chemical shifts; an upfield shift is measured for the ^{31}P chemical shifts on going from **144** to **145**, with the exception of the diastereomeric pair **144a** and **145a** (Table 9). As a consequence of the diastereomeric counterpart not being available, the spatiality of **144d** was assigned purely on the basis of the observed NOE interactions.

As regards the relative configurations **144d**, **144e** and **145e**, the ^3J(H-1,H-11b) couplings are informative. For **144d**, the coupling constant of 9.2 Hz between H-1 and H-11b proves their *trans*-diaxial arrangement. The low ^3J(H-1,H-11b) values of 2.8 and 2.9 Hz observed in **144e** and **145e**, respectively, indicate almost orthogonal geometry for the vicinal protons in question,

proving their *cis*-axial-equatorial relative configuration. In consequence of the synthetic pathway, these are also the relative configurations of the starting diamines **106d** and **106e**.

Table 9. Selected chemical shifts and vicinal coupling constants

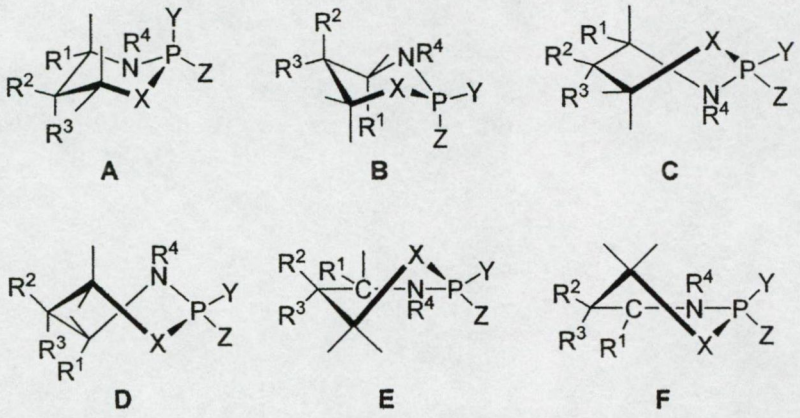
	δ^{31}P	δH2$_{ax}$	δH2$_{eq}$	^3J(H-11b,P)	^3J(H-2$_{ax}$,P)	^3J(H-2$_{eq}$,P)	^3J(H-11b,H-1$_{eq}$)	^3J(H-11b,H-1$_{ax}$)
144a	26.0	3.35	3.44	2.8	5.0	22.1	6.8	9.0
145a	24.9	3.54	3.33	2.9	6.0	21.8	3.3	11.9
144b	22.5	3.89	3.73	3.3	11.3	16.6	5.5	8.8
145b	23.1	4.00	3.63	4.4	6.6	16.2	4.2	10.8
144c	25.2	3.46	3.25	2.6	4.0	17.0	4.4	9.9
145c	29.1	3.54	3.08	2.2	4.7	20.9	2.0	11.6
144d	28.6	2.91	3.47	4.8	10.8	18.6	-	9.2
144e	24.7	3.56	3.23	1.8	3.5	24.3	2.8	-
145e	29.4	3.87	3.11	3.5	5.6	23.5	2.9	-

The chemical shifts (δ) are given in ppm, and the coupling constants (^3J) are given in Hz.

The phosphorus-containing heterocycles are prone to participate in a conformational equilibrium involving chair, twisted chair and other distorted conformations (**A-E**)[14] (Figure 14). This conformational flexibility stems from the greater bond lengths associated with the phosphorus. The straightforward way to obtain information on the conformational equilibria of the model compounds is analysis of the ^3J(P,H) coupling constants, which allows estimation of the dihedral angle distribution by using the following formula:

$$P_B = (^3J_{obs} - ^3J_A)/(^3J_B - ^3J_A), \qquad P_A = 1\text{-}P_B \qquad \text{(Eq. 2)}$$

where P_A and P_B are the populations, $^3J_{obs}$ is the experimentally observed coupling constant, and ^3J_A and ^3J_B are the reference coupling constants in states **A** and **B**, respectively. On the basis of the literature data,[13,14,129,130] estimated reference values of 25 and 3 Hz are chosen for ^3J(P,H$_{eq}$) and ^3J(P,H$_{ax}$), respectively. The low values observed for ^3J(P,H-11b) clearly show its predominantly axial orientation in the diazaphosphinane ring (Table 9), which rules out conformers **B** and **D** containing an equatorial H-11b, and points to conformers **A** and **C**. For **144d** and **145b**, a slightly increased ^3J(P,H-11b) value is observed, suggesting that the conformation reflects a degree of similarity to the flattened ring geometry of **E** and **F**;[14] however, we describe the present diazaphosphinane ring conformations as involving an equilibrium between the idealized conformers **A** and **C**. The estimated ratios are given in Table 10.



Possible conformations of 1,3,2-diazaphosphinanes (X = NR') and the related 1,3,2-oxazaphosphinanes[14] (X = O)

Figure 14

The sum of the conformer populations calculated independently from ^3J(P,H-2_{eq}) and ^3J(P,H-2_{ax}) significantly exceeds 100% for **145b** and **144c**, where N-3 possesses Me or Ph substituents. Such anomalous behaviour of the coupling constants can be explained by the assumption of distorted conformational states differing from **A** and **C**, which might be caused by unfavourable 1,2 interactions between the substituents on N-3 and P.[II]

Table 10. Conformer populations (%)

	[A]	[C]	[A] +[C]
144a	91	13	104
145a	87	15	101
144b	62	38	100
145b	84	40	124
144c	95	36	132
145c	92	19	111
144d	65	29	94
144e	98	3	101
145e	88	7	95

As concerns the conformation of the annelated isoquinoline moiety, the vicinal coupling constants between H-6_{ax} and H-7_{ax} lie in the interval 7.9-11.8 Hz, indicating their diaxial orientation. A NOESY cross-peak between H-11b and H-6_{ax} can be observed for each compound. These spectral parameters render the twist conformation likely for the tetrahydroisoquinoline moiety, which is a general feature of tetrahydroisoquinoline derivatives condensed angularly to a saturated 1,3- or 1,2,3-heterocycle.[12-15]

4. SUMMARY

During my PhD studies, tetrahydroisoquinoline difunctional compounds, diamines and hydrazino alcohols, were prepared and their transformations towards isoquinoline-condensed, saturated 1,2-, 1,2,3- and 1,2,3,4-heterocycles were investigated. Both the ring-chain tautomeric and conformational equilibria of the prepared tricycles were sensitive to the steric and/or electronic effects of the substituents and the relative configurations of the substituted atoms. The main findings are as follows:

1. Starting from homoveratrylamine and *N*-Cbz-protected glycine or β-alanine, 1-aminomethyl- (**11**) and 1-(2′-aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**106a**) were prepared by a convenient four-step process (acylation, BISCHLER-NAPIERALSKI ring-closure, reduction and deprotection). This synthetic method was successfully extended to substituted β-alanine (*N*-phenyl or α-methyl) and homoveratrylamine (α-methyl) derivatives.

   $NaBH_4$ reductions of 1′- or 3-methyl-substituted 1-[2′-(Cbz-amino)ethyl]-6,7-dimethoxy-3,4-dihydroisoquinoline (**104c** and **110**) proved to be highly stereoselective processes yielding 7 : 1 (**105c** : **105d**) or 12 : 1 (**111a** : **111b**) mixtures of the corresponding diastereomers, from which the main products could easily be isolated and converted to the diamines (1*R**,1′*R**)-**106d** and (1*R**,3*S**)-**112**.

   In the case of the 1′-methyl-substituted **104c**, the reducing agent applied and the sequence of the reduction and deprotection steps proved to have marked effects on the formation of the possible diamine diastereomers. Catalytic hydrogenation of the deprotected dihydroisoquinoline **107** in the presence of a Pd/C catalyst resulted in the diamine (1*R**,1′*S**)-**106e** with a high diastereomeric excess.

   The (1*R**,3*R**)-3-methyl-substituted diamine diastereomer **115** and 3-aminomethyl-1,2,3,4-tetrahydroisoquinoline (**13**) were prepared by $LiAlH_4$ reduction of the corresponding known carboxamides (**114** and **117**).

2. By using the two-step procedure (*N*-nitrosation and a subsequent $LiAlH_4$ reduction) usually applied for the synthesis of hydrazine derivatives, 1-hydroxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (calycotomine: **121**) and the regioisomeric 3-hydroxymethyl analogues (**123a,b**) were converted to the corresponding tetrahydroisoquinoline hydrazino alcohols (**14** and **124a,b**).

3. Condensation of the prepared tetrahydroisoquinoline 1,2- and 1,3-diamines containing a primary amino group (**11**, **13**, **106a**, **106d**, **106e**, **112** and **115**), with aromatic aldehydes

resulted in 3-aryl-substituted hexahydroimidazo[5,1-*a*]- (**129**) and [1,5-*b*]isoquinolines (**128**) and 4-aryl-substituted hexahydropyrimido[6,1-*a*]isoquinolines (**130-134**). The ring-chain tautomeric character of the prepared imidazo- and pyrimido-isoquinolines was studied by means of ^{1}H NMR spectroscopy in $CDCl_3$ at 300 K. The ratios of the tautomeric forms were determined by integration of their characteristic protons.

4. Both linear and angular imidazo-isoquinoline derivatives (**128** and **129**) proved to participate in three-component ring-chain tautomeric equilibria, which could be characterized by HAMMETT-type correlations. The relative configuration of the cyclic tautomer was found to exert only a small influence on the values of ρ and the intercept (log $K_{X=H}$) for the equilibria of the angular compounds (**129**), whereas considerable differences in the values of ρ and log $K_{X=H}$ were found for the *cis*-chain (**128B-128A**) and *trans*-chain (**128C-128A**) equilibria of the linear analogues, which could be explained by the different hyperconjugative (anomeric) effects observed between the nitrogen lone pair and the C-3-attached antibonding orbitals in the C-3 epimeric ring forms.

5. The ring-chain tautomeric equilibria of the 1-unsubstituted and 1-methyl-substituted 4-aryl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-pyrimido[6,1-*a*]isoquinolines (**130-132**) were shifted quantitatively towards the cyclic forms, while for the (6*S**,11b*R**)-6-methyl-substituted derivative **133**, the tautomeric equilibrium was shifted quantitatively towards the open tautomer. The ring-chain tautomeric equilibrium of the (6*R**,11b*R**) 6-methyl-substituted derivatives was sensitive to the electronic effects of the 4-aryl substituents and could be characterized by HAMMETT-type equations. The different values of ρ for the *cis*-chain (**134B-134A**) and *trans*-chain (**134C-134A**) equilibria could be rationalized by the different hyperconjugative (anomeric) effects in **134B** and **134C**.

6. The conformational equilibria of *cis*^{1}-*trans*-*cis*^{2} type of the prepared imidazo- and pyrimidoisoquinolines were investigated by NMR and computational methods. For linearly-fused imidazo[1,5-*b*]isoquinolines, *trans*-connected B/C rings were found for both the major and the minor cyclic forms. The preferred conformations of the angular imidazo[5,1-*a*]isoquinoline proved to be dependent on the C-3 configuration: *trans* B/C rings for the minor (**129Be**) and *cis*^{1} B/C rings for the major cyclic form **129Ce**.

   For 4-(*p*-nitrophenyl)hexahydropyrimido[6,1-*a*]isoquinolines, methyl substituents at positions 1 and 6 and the relative configurations of C-1, C-4 and C-11b exerted strong effects on the conformation. The steric hindrance between H-11 and the 1-methyl group or between the 6-methyl and 4-(*p*-nitrophenyl) groups makes the predominant

conformation with *trans*-arranged B/C rings unfavourable and shifts the conformational equilibrium towards the *cis*[1] structure.

7. By *N*-substitution reactions of 1-(Cbz-aminomethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**101**) with isocyanates or isothiocyanates, the corresponding urea or thiourea derivatives were obtained, which were assayed as P-gp inhibitors to determine their MDR reversal activity. Six of the tested compounds were at least as inhibitory as verapamil, a well-known MDR-modulating agent, against P-gp.

8. The hydrazino alcohols **14, 124a,b** and **137** were cyclized with phenylphosphonic dichloride and phenyl dichlorophosphate, resulting in saturated pyrido[1,2-*d*]1,3,4,2-oxadiazaphosphinine-3-oxides (**138** and **139**), 1,3,4,2-oxadiazaphosphino[5,4-*a*]isoquinoline-3-oxides (**140** and **141**) and 1,3,4,2-oxadiazaphosphino[4,5-*b*]isoquinoline-3-oxides (**142** and **143**) as the first representatives of these ring systems.

   By similar ring-closures of diamines **106a-e** with phenylphosphonyc dichloride, 1,3,2-diazaphosphino[6,1-*a*]isoquinolines (**144** and **145**) were prepared. The *N*-substituents proved to have significant effects on the ratios of the diastereomers formed: in the case of the *N*-unsubstituted diamines (**106a,d,e**), the diastereomers containing a 4-phenyl group and H-11b in the *cis* position, were the major isomers, while the *N*-phenyl- and *N*-methyl-substituted diamines (**106b,c**) gave the isomers with the opposite geometry as the main products.

9. The NMR and X-ray conformation analysis on **138-143** revealed that, independently of the *P*-substituent and the relative configuration of the phosphorus atom, **138-141** could be characterized by *trans*-connected hetero rings and the chair conformation of the 1,3,4,2-oxadiazaphosphinane moiety, while the stereochemistry of the connection of the hetero rings (*trans* or *cis*[2]) was found to be dependent on the *P*-configuration relative to that of the carbon at the annelation in the case of 1,3,4,2-oxadiazaphosphinanes linearly fused to tetrahydroisoquinoline (**142** and **143**).

   Conformational analysis of **144** and **145** led to the conclusion that H-an (H-11b) takes up an axial position (relative to the 1,3,2-diazaphosphinane ring) in each case and the conformational behaviour of these compounds can be characterized by the equilibria of conformers having a chair and a twisted chair 1,3,2-diazaphosphinane ring. The conformer populations were also influenced by the substituents at positions 1 and 3, and by the relative configurations of C-11b and C-1 or P-4.

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7. ANNEX